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(54) Title: METHODS OF DIAGNOSIS AND PROGNOSIS OF OVARIAN CANCER

(57) Abstract: The present invention provides novel genes and proteins for diagnosing ovarian cancer and/or a likelihood for survival, or recurrence of disease, wherein the expression of the genes and proteins is up-regulated or down-regulated or associated with the occurrence or recurrence of a specific scanner sub-type. The ovarian cancer-associated genes and proteins of the invention are specifically exemplified by the genes and proteins set forth in Tables 1 to 3 and the Sequence Listing.

WO 2004/022778 A1

METHODS OF DIAGNOSIS AND PROGNOSIS OF OVARIAN CANCER

Field of the invention

The present invention relates to the identification of nucleic acid and protein expression
5 profiles and nucleic acids, products, and antibodies thereto that are involved in ovarian
cancer; and to the use of such expression profiles and compositions in the diagnosis,
prognosis and therapy of ovarian cancer. More particularly, this invention relates to
novel genes that are expressed at elevated or reduced levels in malignant tissues and
uses therefor in the diagnosis of cancer or malignant tumors in human subjects. This
10 invention also relates to the use of nucleic acid or antibody probes to specifically detect
ovarian cancer cells, such as, for example, in the ovarian surface epithelium, wherein
over-expression or reduced expression of nucleic acids hybridizing to the probes is highly
associated with the occurrence and/or recurrence of an ovarian tumor, and/or the
likelihood of patient survival. The diagnostic and prognostic test of the present invention
15 is particularly useful for the early detection of ovarian cancer or metastases thereof, or
other cancers, and for monitoring the progress of disease, such as, for example, during
remission or following surgery or chemotherapy. The present invention is also directed
to methods of therapy wherein the activity of a protein encoded by a
diagnostic/prognostic gene described herein is modulated.

20

Background of the invention1. *General*

As used herein the term "derived from" shall be taken to indicate that a specified integer
are obtained from a particular source albeit not necessarily directly from that source.

25

Unless the context requires otherwise or specifically stated to the contrary, integers,
steps, or elements of the invention recited herein as singular integers, steps or elements
clearly encompass both singular and plural forms of the recited integers, steps or
elements.

30

The embodiments of the invention described herein with respect to any single
embodiment shall be taken to apply *mutatis mutandis* to any other embodiment of the
invention described herein.

Throughout this specification, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated step or element or integer or group of steps or elements or integers but not the exclusion of any other step or element or integer or group of elements or integers.

Those skilled in the art will appreciate that the invention described herein is susceptible to variations and modifications other than those specifically described. It is to be understood that the invention includes all such variations and modifications. The invention also includes all of the steps, features, compositions and compounds referred to or indicated in this specification, individually or collectively, and any and all combinations or any two or more of said steps or features.

The present invention is not to be limited in scope by the specific examples described herein. Functionally equivalent products, compositions and methods are clearly within the scope of the invention, as described herein.

The present invention is performed without undue experimentation using, unless otherwise indicated, conventional techniques of molecular biology, microbiology, virology, recombining DNA technology, peptide synthesis in solution, solid phase peptide synthesis, and immunology. Such procedures are described, for example, in the following texts that are incorporated herein by reference:

1. Sambrook, Fritsch & Maniatis, *Molecular Cloning: A Laboratory Manual*, Cold Spring Harbor Laboratories, New York; Second Edition (1989), whole of Vols I, II, and III;
2. *DNA Cloning: A Practical Approach*, Vols. I and II (D. N. Glover, ed., 1985), IRL Press, Oxford, whole of text;
3. *Oligonucleotide Synthesis: A Practical Approach* (M. J. Gait, ed., 1984) IRL Press, Oxford, whole of text, and particularly the papers therein by Gait, pp1-22; Atkinson *et al.*, pp35-81; Sproat *et al.*, pp 83-115; and Wu *et al.*, pp 135-151;
4. *Nucleic Acid Hybridization: A Practical Approach* (B. D. Hames & S. J. Higgins, eds., 1985) IRL Press, Oxford, whole of text;
5. Perbal, B., *A Practical Guide to Molecular Cloning* (1984);
6. Wünsch, E., ed. (1974) *Synthese von Peptiden in Houben-Weyls Methoden der Organischen Chemie* (Müller, E., ed.), vol. 15, 4th edn., Parts 1 and 2, Thieme, Stuttgart.

7. Handbook of Experimental Immunology, Vols. I-IV (D. M. Weir and C. C. Blackwell, eds., 1986, Blackwell Scientific Publications).

5 This specification contains nucleotide and amino acid sequence information prepared using PatentIn Version 3.1, presented herein after the claims. Each nucleotide sequence is identified in the sequence listing by the numeric indicator <210> followed by the sequence identifier (e.g. <210>1, <210>2, <210>3, etc). The length and type of sequence (DNA, protein (PRT), etc), and source organism for each nucleotide sequence, are indicated by information provided in the numeric indicator fields <211>, <212> and
10 <213>, respectively. Nucleotide sequences referred to in the specification are defined by the term "SEQ ID NO:", followed by the sequence identifier (eg. SEQ ID NO: 1 refers to the sequence in the sequence listing designated as <400>1).

15 The designation of nucleotide residues referred to herein are those recommended by the IUPAC-IUB Biochemical Nomenclature Commission, wherein A represents Adenine, C represents Cytosine, G represents Guanine, T represents thymine, Y represents a pyrimidine residue, R represents a purine residue, M represents Adenine or Cytosine, K represents Guanine or Thymine, S represents Guanine or Cytosine, W represents Adenine or Thymine, H represents a nucleotide other than Guanine, B represents a
20 nucleotide other than Adenine, V represents a nucleotide other than Thymine, D represents a nucleotide other than Cytosine and N represents any nucleotide residue.

2. *Description of the related art*

25 Cancer is a multi-factorial disease and major cause of morbidity in humans and other animals, and deaths resulting from cancer in humans are increasing and expected to surpass deaths from heart disease in future. Carcinomas of the lung, prostate, breast, colon, pancreas, and ovary are major contributing factors to total cancer death in humans. For example, prostate cancer is the fourth most prevalent cancer and the second leading cause of cancer death in males. Similarly, cancer of the ovary is the
30 second most common cancer of the female reproductive organs and the fourth most common cause of cancer death among females. With few exceptions, metastatic disease from carcinoma is fatal. Even if patients survive their primary cancers, recurrence or metastases are common.

35 It is widely recognized that simple and rapid tests for solid cancers or tumors have considerable clinical potential. Not only can such tests be used for the early diagnosis of

cancer but they also allow the detection of tumor recurrence following surgery and chemotherapy. A number of cancer-specific blood tests have been developed which depend upon the detection of tumor-specific antigens in the circulation (Catalona, W.J., *et al.*, 1991, "Measurement of prostate-specific antigen in serum as a screening test for prostate cancer", *N. Engl. J. Med.* 324, 1156-1161; Barrenetxea, G., *et al.*, 1998, "Use of serum tumor markers for the diagnosis and follow-up of breast cancer", *Oncology*, 55, 447-449; Cairns, P., and Sidransky, D., 1999, "Molecular methods for the diagnosis of cancer". *Biochim. Biophys. Acta.* 1423, C 11-C 18).

10 Ovarian cancer is the fourth most frequent cause of cancer death in females and in the United States, and accounts for approximately 13,000 deaths annually. Furthermore, ovarian cancer remains the number one killer of women with gynaecological malignant hyperplasia and the incidence is rising in industrialized countries. The etiology of the neoplastic transformation remains unknown although there is epidemiological evidence
15 for an association with disordered endocrine function. The incidence of ovarian carcinoma is higher in nulliparous females and in those with early menopause.

Most ovarian cancers are thought to arise from the ovarian surface of epithelium (OSE). Epithelial ovarian cancer is seldom encountered in women less than 35 years of age. Its
20 incidence increases sharply with advancing age and peaks at ages 75 to 80, with the median age being 60 years. The single most important known risk factor is a strong familial history of breast or ovarian cancer. To date, little is known about the structure and function of the OSE cells. It is known that the OSE is highly dynamic tissue that undergoes morphogenic changes, and has proliferative properties sufficient to cover the
25 ovulatory site following ovulation. Morphological and histochemical studies suggest that the OSE has secretory, endocytotic and transport functions which are hormonally-controlled (Blaustein and Lee, *Oncol.* 8, 34-43, 1979; Nicosia and Johnson, *Int. J. Gynecol. Pathol.*, 3, 249-260, 1983; Papadaki and Beilby, *J. Cell Sci.* 8, 445-464, 1971; Anderson *et al.*, *J. Morphol.*, 150, 135-164, 1976).

30 Ovarian cancers are not readily detectable by diagnostic techniques (Siemens *et al.*, *J. Cell. Physiol.*, 134: 347-356, 1988). In fact, the diagnosis of carcinoma of the ovary is generally only possible when the disease has progressed to a late stage of development. Approximately 75% of women diagnosed with ovarian cancer are already at an advanced
35 stage (III and IV) of the disease at their initial diagnosis. During the past 20 years, neither diagnosis nor five year survival rates have greatly improved for these patients. This is

substantially due to the high percentage of high-stage initial detection of the disease. There is therefore a need to develop new markers that improve early diagnosis and thereby reduce the percentage of high-stage initial diagnoses.

- 5 A number of proteinaceous ovarian tumor markers were evaluated several years ago, however these were found to be non-specific, and determined to be of low value as markers for primary ovarian cancer (Kudlacek *et al.*, *Gyn. Onc.* 35, 323-329, 1989; Rustin *et al.*, *J. Clin. Onc.*, 7, 1667-1671, 1989; Sevela *et al.*, *Am. J. Obstet. Gynecol.*, 161, 1213-1216, 1989; Omar *et al.*, *Tumor Biol.*, 10, 316-323, 1989). Several
10 monoclonal antibodies were also shown to react with ovarian tumor associated antigens, however they were not specific for ovarian cancer and merely recognize determinants associated with high molecular weight mucin-like glycoproteins (Kenemans *et al.*, *Eur. J. Obstet. Gynecol. Reprod. Biol.* 29, 207-218, 1989; McDuffy, *Ann. Clin. Biochem.*, 26, 379-387, 1989). More recently, oncogenes associated with ovarian cancers have been
15 identified, including *HER-2/neu (c-erbB-2)* which is over-expressed in one-third of ovarian cancers (USPN 6,075,122 by Cheever *et al.*, issued June 13, 2000), the *fms* oncogene, and abnormalities in the *p53* gene, which are seen in about half of ovarian cancers.

- Whilst previously identified markers for carcinomas of the ovary have facilitated efforts to
20 diagnose and treat these serious diseases, there is a clear need for the identification of additional markers and therapeutic targets. The identification of tumor markers that are amenable to the early-stage detection of localized tumors is critical for more effective management of carcinomas of the ovary.

25 Summary of the invention

- In work leading up to the present invention, the inventors sought to identify nucleic acid markers that were diagnostic of ovarian cancers generally, or diagnostic of specific ovarian cancers such as, for example, serous ovarian cancer (SOC), mucinous ovarian cancer (MOC), non-invasive (borderline ovarian cancer or low malignant potential
30 ovarian cancer), mixed phenotype ovarian cancer, endometrioid ovarian cancer (EnOC) and clear cell ovarian cancer (CICA), papillary serous ovarian cancer, Brenner cell or undifferentiated adenocarcinoma, by virtue of their modulated expression in cancer tissues derived from a patient cohort compared to their expression in healthy or non-cancerous cells and tissues. Additionally, the inventors sought to determine whether any
35 correlation exists between the expression of any particular gene in a subject having ovarian cancer and the survival, or likelihood for survival, of the subject during the

medium to long term (i.e. in the period between about 1-2 years from primary diagnosis, or longer). The inventors also sought to determine whether any correlation exists between the expression of any particular gene in a subject following treatment for ovarian cancer and the recurrence, or likelihood for recurrence, of ovarian cancer in the subject during the medium to long term (i.e. in the period between about 1-2 years from primary diagnosis, or longer).

As exemplified herein, the inventors identified a number of genes whose expression is altered (up-regulated or down-regulated) in individuals with ovarian cancer compared to healthy individuals., eg., subjects who do not have ovarian cancer. The particular genes are identified in Tables 1 and 2. Preferably, the genes are selected from the group of candidate genes set forth in Table 3.

The list of genes and proteins exemplified herein by Table 1 were identified by a statistical analysis as outlined in the examples which gave a P-value, eg., by comparison of expression to the expression of that gene in normal ovaries.

Accordingly, one aspect of the present invention provides a method of detecting an ovarian cancer-associated transcript in a biological sample, the method comprising contacting the biological sample with a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Table 1 or 2 or 3. Preferably the percentage identity to a sequence disclosed in any one of Tables 1-3 is at least about 85% or 90% or 95%, and still more preferably at least about 98% or 99%.

In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a modified level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- (iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- (iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 47, 49, 51, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and
- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a modified level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- (iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27,

29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

- (iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 47, 49, 51, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and
- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

Even more preferably, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a modified level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- (iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- (iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 6, 8, 10, 12, 14, 16, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 47, 49, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and
- (v) a sequence that is complementary to (i) or (ii) or (iii) or (iv).

As used herein, the term "modified level" includes an enhanced, increased or elevated level of an integer being assayed, or alternatively, a reduced or decreased level of an integer being assayed.

- 5 In one embodiment an elevated, enhanced or increased level of expression of the nucleic acid is detected. In accordance with this embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and
- 10 then detecting the hybridization wherein an enhanced level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:
- 15 (i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;
 - (ii) a sequence that hybridizes under at least low stringency hybridization conditions
 - 20 to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;
 - (iii) a sequence that is at least about 80% identical to (i) or (ii);
 - 25 (iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200; and
 - (v) a sequence that is complementary to any one of the sequences set forth in (i) or
 - 30 (ii) or (iii) or (iv).

In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe

35 for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an enhanced level of hybridization of the probe for the subject

being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- 5 (i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- 10 (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- 15 (iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- 20 (iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 10, 12, 14, 16, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 47, 49, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and
- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

- 25 In an alternative preferred embodiment, a reduced level of a diagnostic marker is indicative of ovarian cancer. In accordance with this embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for
- 30 hybridization to occur and then detecting the hybridization wherein a reduced level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;
 - (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;
 - (iii) a sequence that is at least about 80% identical to (i) or (ii);
 - (iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200; and
 - (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).
- 15 In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a reduced level of hybridization of the probe for the subject being
- 20 tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:
- (i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, and 5;
 - (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, and 5;
 - (iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 1, 3, and 5;
 - (iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, and 6; and
 - (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).
- 35 Preferably, the ovarian cancer that is diagnosed according to the present invention is an epithelial ovarian cancer, such as, for example, serous ovarian cancer, non-invasive

ovarian cancer, mixed phenotypic ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer, clear cell ovarian cancer, papillary serous ovarian cancer, Brenner cell or undifferentiated adenocarcinoma. As will be apparent from the preferred embodiments described below, certain of the genes represented in Table 1, Table 2 and
5 Table 3 are expressed at modified levels in subjects having serous or mucinous ovarian cancers. Data presented in Figures 1-4 also exemplify novel diagnostics and prognostics for serous ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer and clear cell ovarian cancer.

10 As exemplified herein by Table 2, the present inventors have identified those genes having an elevated or reduced average ratio of expression of specific genes between ovarian cancer patients vs non-ovarian cancer patients, wherein a high ratio in Table 2 indicates an enhanced expression in an ovarian cancer patients and wherein a negative ratio indicates that a reduced expression in an ovarian cancer patient.

15

In an alternative preferred embodiment, the present invention provides a method of diagnosing a serous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and
20 then detecting the hybridization wherein a modified level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a serous ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- 25 (i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession Number selected from the group consisting of: U62801, D49441, X51630, and AB018305;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions
30 to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession Number selected from the group consisting of: U62801, D49441, X51630, And AB018305;
- (iii) a sequence that is at least about 80% identical to (i) or (ii);
- (iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in
35 Table 2 or as set forth in Table 1 and having an Accession Number selected from the group consisting of: U62801, D49441, X51630, And AB018305; and

- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

In a further alternative preferred embodiment, the present invention provides a method of
 5 diagnosing a mucinous ovarian cancer in a human or animal subject being tested said
 method comprising contacting a biological sample from said subject being tested with a
 nucleic acid probe for a time and under conditions sufficient for hybridization to occur and
 then detecting the hybridization wherein an elevated level of hybridization of the probe for
 the subject being tested compared to the hybridization obtained for a control subject not
 10 having ovarian cancer indicates that the subject being tested has a mucinous ovarian
 cancer, and wherein said nucleic acid probe comprises a sequence selected from the
 group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic
 acid set forth in Table 1 and having an Accession Number selected from the group
 15 consisting of: NM_006149, AA315933, U47732, NM_005588, AW503395,
 NM_004063, AI073913, AI928445, NM_022454, W40460, AA132961 and
 AF111856;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions
 to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1
 20 and having an Accession Number selected from the group consisting of:
 NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063,
 AI073913, AI928445, NM_022454, W40460, AA132961 and AF111856;
- (iii) a sequence that is at least about 80% identical to (i) or (ii);
- (iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in
 25 Table 1 and having an Accession Number selected from the group consisting of:
 NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063,
 AI073913, AI928445, NM_022454, W40460, AA132961 and AF111856; and
- (v) a sequence that is complementary to any one of the sequences set forth in (i) or
 (ii) or (iii) or (iv).

30

In a preferred embodiment, the present invention provides a method of diagnosing a
 mucinous ovarian cancer in a human or animal subject being tested said method
 comprising contacting a biological sample from said subject being tested with a nucleic
 acid probe for a time and under conditions sufficient for hybridization to occur and then
 35 detecting the hybridization wherein an enhanced level of hybridization of the probe for
 the subject being tested compared to the hybridization obtained for a control subject not

having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- 5 (i) a sequence comprising at least about 20 contiguous nucleotides from SEQ ID NO: 57 or 59 or 61;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from SEQ ID NO: 57 or 59 or 61;
- (iii) a sequence that is at least about 80% identical to SEQ ID NO: 57 or 59 or 61;
- (iv) a sequence that encodes the amino acid sequence set forth in SEQ ID NO: 58 or
10 60 or 62; and
- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

Those skilled in the art will be aware that as a carcinoma progresses, metastases occur
15 in organs and tissues outside the site of the primary tumor. For example, in the case of ovarian cancer, metastases commonly appear in a tissue selected from the group consisting of omentum, abdominal fluid, lymph nodes, lung, liver, brain, and bone. Accordingly, the term "ovarian cancer" as used herein shall be taken to include an early or developed tumor of the ovary, such as, for example, any one or more of a number of
20 cancers of epithelial origin, such as serous, mucinous, endometrioid, clear cell, papillary serous, Brenner cell or undifferentiated adenocarcinoma, non-invasive ovarian cancer such as borderline ovarian cancer or low-malignant potential ovarian cancer, or a mixed phenotype ovarian cancer, and optionally, any metastases outside the ovary that occurs in a subject having a primary tumor of the ovary.

25 As used herein, the term "diagnosis", and variants thereof, such as, but not limited to "diagnose", "diagnosed" or "diagnosing" shall not be limited to a primary diagnosis of a clinical state, however should be taken to include any primary diagnosis or prognosis of a clinical state. For example, the "diagnostic assay" formats described herein are equally
30 relevant to assessing the remission of a patient, or monitoring disease recurrence, or tumor recurrence, such as following surgery or chemotherapy, or determining the appearance of metastases of a primary tumor. All such uses of the assays described herein are encompassed by the present invention.

35 Both classical hybridization and amplification formats, and combinations thereof, are encompassed by the invention. In one embodiment, the hybridization comprises

performing a nucleic acid hybridization reaction between a labeled probe and a second nucleic acid in the biological sample from the subject being tested, and detecting the label. In another embodiment, the hybridization comprising performing a nucleic acid amplification reaction eg., polymerase chain reaction (PCR), wherein the probe consists of a nucleic acid primer and nucleic acid copies of the nucleic acid in the biological sample are amplified. As will be known to the skilled artisan, amplification may proceed classical nucleic acid hybridization detection systems, to enhance specificity of detection, particularly in the case of less abundant mRNA species in the sample.

10 In a preferred embodiment, the polynucleotide is immobilised on a solid surface.

The present invention clearly encompasses nucleic acid-based methods and protein-based methods for diagnosing cancer in humans and other mammals.

15 Accordingly, in a related embodiment, the present invention provides a method of detecting an ovarian cancer-associated polypeptide in a biological sample the method comprising contacting the biological sample with an antibody that binds specifically to an ovarian cancer-associated polypeptide in the biological sample, the polypeptide being encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3.

Preferably the percentage identity to a sequence disclosed in any one of Tables 1-3 is at least about 85% or 90% or 95%, and still more preferably at least about 98% or 99%.

25 In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a modified level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34,

36, 38, 40, 42, 44, 47, 49, 51, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising
5 contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a modified level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for
10 a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 2, 6, 8, 10, 12, 14, 16, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38,
15 40, 42, 47, 49, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

In one embodiment an elevated, enhanced or increased level of expression of the antigen-antibody complex is detected. In accordance with this embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal
20 subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian
25 cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200.

30

In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising
contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then
35 detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for

a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 47, 49, 51, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

In an alternative preferred embodiment, a reduced level of a diagnostic marker is indicative of ovarian cancer. In accordance with this embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a reduced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200.

In a preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a reduced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 2, 4, and 6.

Preferably, the ovarian cancer that is diagnosed according to the present invention is an epithelial ovarian cancer, such as, for example, serous ovarian cancer or mucinous ovarian cancer.

In an alternative preferred embodiment, the present invention provides a method of diagnosing a serous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a modified level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a serous ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession Number selected from the group consisting of: U62801, D49441, X51630, And AB018305.

In a further alternative preferred embodiment, the present invention provides a method of diagnosing a mucinous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a reduced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a mucinous ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063, AI073913, AI928445, NM_022454, W40460, AA132961 and AF111856.

In a preferred embodiment, the present invention provides a method of diagnosing a mucinous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a mucinous ovarian cancer, and wherein said antibody binds to a

polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to SEQ ID NO: 58 or 60 or 62.

- 5 In a further related embodiment, the present invention provides a method of detecting an ovarian cancer-associated antibody in a biological sample the method comprising contacting the biological sample with a polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3, wherein the polypeptide specifically binds to the ovarian cancer-associated
10 antibody.

Preferably, in the above methods, the biological sample is contacted with a plurality of the polynucleotides, polypeptides or antibodies referred to above.

- 15 In a particularly preferred embodiment, the present invention provides an antibody-based multiplex assay for determining the likelihood of survival of a subject from an ovarian cancer. In one embodiment, the invention provides a method of determining the likelihood of survival of a subject suffering from a serous ovarian cancer, said method comprising contacting a biological sample from said subject being tested with at least two
20 antibodies for a time and under conditions sufficient for antigen-antibody complexes to form and then detecting the complexes wherein an enhanced level of the antigen-antibody complexes for the subject being tested compared to the amount of the antigen-antibody complexes formed for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein one antibody
25 binds to an sFRP polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 72 and wherein one antibody binds to a SOCS3 polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 74.

- The present invention is not to be limited by the source or nature of the biological
30 sample. In one embodiment, the biological sample is from a patient undergoing a therapeutic regimen to treat ovarian cancer. In an alternative preferred embodiment, the biological sample is from a patient suspected of having ovarian cancer.

- In addition to providing up-regulated and down-regulated genes, the list of genes and
35 proteins exemplified herein by Table 1 were identified by a statistical analysis as outlined in the examples which gave a P-value, eg., by comparison of expression to

clinicopathological parameters for disease recurrence or patient survival. Accordingly, the present invention is particularly useful for prognostic applications, in particular for assessing the medium-to-long term survival of a subject having an ovarian cancer, or alternatively or in addition, for assessing the likelihood of disease recurrence.

5

Accordingly, a further aspect of the present invention provides a method of monitoring the efficacy of a therapeutic treatment of ovarian cancer, the method comprising:

- (i) providing a biological sample from a patient undergoing the therapeutic treatment; and
- 10 (ii) determining the level of a ovarian cancer-associated transcript in the biological sample by contacting the biological sample with a polynucleotide that selectively hybridizes to a sequence having at least about 80% identity to a sequence as shown in any one of Tables 1-3, thereby monitoring the efficacy of the therapy.

15

Preferably the method further comprises comparing the level of the ovarian cancer-associated transcript to a level of the ovarian cancer-associated transcript in a biological sample from the patient prior to, or earlier in, the therapeutic treatment.

20 In a related embodiment, the present invention provides a method of monitoring the efficacy of a therapeutic treatment of ovarian cancer, the method comprising :

- (i) providing a biological sample from a patient undergoing the therapeutic treatment; and
- 25 (ii) determining the level of a ovarian cancer-associated antibody in the biological sample by contacting the biological sample with a polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3, wherein the polypeptide specifically binds to the ovarian cancer-associated antibody, thereby monitoring the efficacy of the therapy.

30

Preferably the method further comprises comparing the level of the ovarian cancer-associated antibody to a level of the ovarian cancer-associated antibody in a biological sample from the patient prior to, or earlier in, the therapeutic treatment.

In a further related embodiment, the present invention provides a method of monitoring the efficacy of a therapeutic treatment of ovarian cancer, the method comprising :

- (i) providing a biological sample from a patient undergoing the therapeutic treatment; and
- 5 (ii) determining the level of a ovarian cancer-associated polypeptide in the biological sample by contacting the biological sample with an antibody, wherein the antibody specifically binds to a polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3, thereby monitoring the efficacy of the therapy.

10

Preferably the method further comprises comparing the level of the ovarian cancer-associated polypeptide to a level of the ovarian cancer-associated polypeptide in a biological sample from the patient prior to, or earlier in, the therapeutic treatment.

- 15 It will also be apparent from the following preferred embodiments, that the expression of certain genes listed in Table 1 and Table 3 is statistically correlated with survival and death of patients having ovarian cancer, wherein a low P value indicates an enhanced likelihood that a patient having altered expression of the gene will die from the cancer.

- 20 Accordingly, in one embodiment, the present invention provides a method of determining the likelihood of survival of a subject suffering from an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the
- 25 subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196,
- 30 AI796870, X02761, AW968613, AW972565, AF045229, AW953853, U52426,
- 35 F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602,

- AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135, BE466173, AI354722, M90464, AA829286, AI333771, BE465867, NM_014992, BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122, AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761, AW968613, AW972565, AF045229, AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602, AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135, BE466173, AI354722, M90464, AA829286, AI333771, BE465867, NM_014992, BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122, AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955;
- (iii) a sequence that is at least about 80% identical to (i) or (ii);
- (iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761, AW968613, AW972565, AF045229, AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602, AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135, BE466173, AI354722,

M90464, AA829286, AI333771, BE465867, NM_014992, BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122, AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, 5 BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955; and

- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

10 In a preferred embodiment, the present invention provides a method of determining the likelihood of survival of a subject suffering from an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the 15 subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from a sequence 20 selected from the group consisting of SEQ ID NOs: 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- 25 (iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- (iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and
- (v) a sequence that is complementary to (i) or (ii) or (iii) or (iv).

30

In an alternative preferred embodiment, the present invention provides a method of determining the likelihood of survival of a subject suffering from an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to 35 form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody

complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence encoded by a nucleic acid set forth in Table 1 and

5 having an Accession Number selected from the group consisting of: NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761, AW968613, AW972565, AF045229,

10 AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602, AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135, BE466173, AI354722, M90464, AA829286, AI333771, BE465867, NM_014992, BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567,

15 AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122, AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955.

20 In an alternative preferred embodiment, the present invention provides a method of determining the likelihood of survival of a subject suffering from an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody

25 complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence

30 selected from the group consisting of SEQ ID NOs: 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

In a particularly preferred embodiment, the present invention provides a marker for determining the likelihood of a subject surviving from serous cancer. In accordance with

35 this embodiment of the invention, there is provided a method of determining the likelihood of survival of a subject suffering from a serous ovarian cancer, said method

comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 71 or 73;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 71 or 73;
- (iii) a sequence that is at least about 80% identical to (i) or (ii) and encoding an sFRP protein or a SOCS3 protein;
- (iv) a sequence that encodes a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 72 or 74; and
- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

In an alternative preferred embodiment, the present invention provides a method of determining the likelihood of survival of a subject suffering from a serous ovarian cancer, said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said antibody binds to an sFRP polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 72 or a SOCS3 polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 74 or.

It will also be apparent from the following preferred embodiments, that the expression of certain genes listed in Table 1 and Table 3 is statistically correlated with recurrence of ovarian cancer, wherein a low P value indicates an enhanced likelihood that a patient having altered expression of the gene will experience recurrence of the disease.

In yet another preferred embodiment, the present invention provides a method of determining the likelihood that a subject will suffer from a recurrence of an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a high probability of recurrence, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- 10 (i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: M86849, AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, 15 BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343, NM_002514, AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393, H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, 20 BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512, AW953853, AU076611, AW968613, AL353944, BE614149, AA292998, H12912, AA188763, AK000596, AI970797, AW519204, Z42387, AF145713, AA972412, AK001564, AW959861, BE313555, W25005, AI193356, AF111106, AI130740, AA985190, BE221880, AF084545, R26584, AW247380, AA364261, U25849, 25 AF262992, AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237, NM_000636, AA130986, AA216363, AA628980, AA811657, AA897108, AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248, AK002039, AL109791, AW090198, AW296454, AW445034, AW452948, AW470411, AW885727, AW970859, AW979189, BE165866, 30 BE175582, BE242587, BE271927, BE439580, BE464016, D63216, F34856, M83822, N33937, N49068, N51357, N80486, NM_000954, NM_005756, NM_016652, R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and Z45051,
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: M86849, 35

- AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343, NM_002514,
- 5 AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393, H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512, AW953853,
- 10 AU076611, AW968613, AL353944, BE614149, AA292998, H12912, AA188763, AK000596, AI970797, AW519204, Z42387, AF145713, AA972412, AK001564, AW959861, BE313555, W25005, AI193356, AF111106, AI130740, AA985190, BE221880, AF084545, R26584, AW247380, AA364261, U25849, AF262992, AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237,
- 15 NM_000636, AA130986, AA216363, AA628980, AA811657, AA897108, AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248, AK002039, AL109791, AW090198, AW296454, AW445034, AW452948, AW470411, AW885727, AW970859, AW979189, BE165866, BE175582, BE242587, BE271927, BE439580, BE464016, D63216, F34856, M83822,
- 20 N33937, N49068, N51357, N80486, NM_000954, NM_005756, NM_016652, R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and Z45051;
- (iii) a sequence that is at least about 80% identical to (i) or (ii);
- (iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in
- 25 Table 1 and having an Accession Number selected from the group consisting of: M86849, AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343,
- 30 NM_002514, AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393, H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512,
- 35 AW953853, AU076611, AW968613, AL353944, BE614149, AA292998, H12912, AA188763, AK000596, AI970797, AW519204, Z42387, AF145713, AA972412,

AK001564, AW959861, BE313555, W25005, AI193356, AF111106, AI130740, AA985190, BE221880, AF084545, R26584, AW247380, AA364261, U25849, AF262992, AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237, NM_000636, AA130986, AA216363, AA628980, AA811657, 5 AA897108, AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248, AK002039, AL109791, AW090198, AW296454, AW445034, AW452948, AW470411, AW885727, AW970859, AW979189, BE165866, BE175582, BE242587, BE271927, BE439580, BE464016, D63216, F34856, M83822, N33937, N49068, N51357, N80486, NM_000954, NM_005756, 10 NM_016652, R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and Z45051; and

(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

15 In an alternative preferred embodiment, the present invention provides a method of determining the likelihood that a subject will suffer from a recurrence of an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the 20 antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a high probability of recurrence, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence encoded by a nucleic acid 25 set forth in Table 1 and having an Accession Number selected from the group consisting of: M86849, AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343, NM_002514, 30 AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393, H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512, AW953853, AU076611, AW968613, AL353944, 35 BE614149, AA292998, H12912, AA188763, AK000596, AI970797, AW519204, Z42387, AF145713, AA972412, AK001564, AW959861, BE313555, W25005, AI193356,

AF111106, AI130740, AA985190, BE221880, AF084545, R26584, AW247380, AA364261, U25849, AF262992, AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237, NM_000636, AA130986, AA216363, AA628980, AA811657, AA897108, AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248, AK002039, AL109791, AW090198, AW296454, AW445034, AW452948, AW470411, AW885727, AW970859, AW979189, BE165866, BE175582, BE242587, BE271927, BE439580, BE464016, D63216, F34856, M83822, N33937, N49068, N51357, N80486, NM_000954, NM_005756, NM_016652, R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and Z45051.

The recurrence of ovarian cancer is a clinical recurrence as determined by the presence of one or more clinical symptoms of an ovarian cancer, such as, for example, a metastases, or alternatively, as determined in a biochemical test, immunological test or serological test such as, for example, a cross-reactivity in a biological sample to a CA125 antibody.

Preferably, the recurrence is capable of being detected at least about 2 years from treatment, more preferably about 2-3 years from treatment, and even more preferably about 4 or 5 or 10 years from treatment.

Preferably, in the above diagnostic and/or prognostic methods, the biological sample is contacted with a plurality of the nucleic acids and/or polypeptides and/or antibodies referred to above. In a particularly preferred embodiment, multiplex assays are performed to detect enhanced expression at least of sFRP4 and SOC3 at the protein level (eg., using antigen-based or antibody-based assays) or at the mRNA level (eg., by detecting elevated levels of mRNA transcripts).

A further embodiment of the present invention provides a method of diagnosing epithelial ovarian cancer by detecting aberrant methylation of a promoter that regulates expression of a tumor suppressor gene eg., MCC. In particular, the present invention contemplates the detection of hypermethylation of the promoter of a tumor suppressor gene. Without being bound by any theory or mode of action, such hypermethylation leads to gene inactivation, thereby reducing expression of the tumor suppressor gene and permitting oncogenesis. In one preferred embodiment, the present invention provides a method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising determining aberrant methylation in a promoter sequence that regulates

expression of a tumor suppressor gene in a biological sample from said subject compared to the methylation of the promoter in nucleic acid obtained for a control subject not having ovarian cancer wherein said aberrant methylation indicates that the subject being tested has an ovarian ovarian cancer.

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In a further aspect, the present invention provides a method for identifying a compound that modulates an ovarian cancer-associated polypeptide, the method comprising :

- (i) contacting the compound with a ovarian cancer-associated polypeptide, the polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3; and
- (ii) determining the functional effect of the compound upon the polypeptide.

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The functional effect may, for example, be a physical effect or a chemical effect. In one embodiment, the functional effect is determined by measuring ligand binding to the polypeptide. In a particular embodiment, the polypeptide is expressed in a eukaryotic host cell or cell membrane. Preferably the polypeptide is recombinant.

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In another aspect, the present invention provides a method of inhibiting proliferation of a ovarian tumour cell, which method comprises contacting said cell with a compound identified using the method *supra* for identifying a compound that modulates an ovarian cancer-associated polypeptide.

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In a further aspect, the present invention provides a method of inhibiting proliferation of a ovarian cancer-associated cell to treat ovarian cancer in a patient, the method comprising the step of administering to the patient a therapeutically effective amount of a compound identified using the method *supra* for identifying a compound that modulates an ovarian cancer-associated polypeptide.

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In a further aspect, the present invention provides a drug screening assay comprising :

- (i) administering a test compound to a mammal having ovarian cancer or a cell isolated therefrom;
- (ii) comparing the level of gene expression of a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3 in a treated cell or mammal with the level of gene expression of the polynucleotide in a control cell or mammal, wherein a test compound that

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modulates the level of expression of the polynucleotide is a candidate for the treatment of ovarian cancer.

Typically, the control is a mammal with ovarian cancer or a cell therefrom that has not
5 been treated with the test compound. Alternatively, the control is a normal cell or mammal.

The present invention also provides a method for treating a mammal having ovarian cancer comprising administering a compound identified the drug screening method
10 *supra*.

In a further aspect, the present invention provides a pharmaceutical composition for use in treating a mammal having ovarian cancer, the composition comprising a compound identified the screening method *supra* for identifying a compound that modulates an
15 ovarian cancer-associated polypeptide, or alternatively, using the drug screening method *supra*, and a physiologically acceptable carrier or diluent.

In a further aspect, the present invention provides an assay device, preferably for use in the diagnosis or prognosis of ovarian cancer, said device comprising a plurality of
20 polynucleotides immobilized to a solid phase, wherein each of said polynucleotides consists of a gene as listed in any one of Tables 1-3. Preferably, the solid phase is a substantially planar chip.

In a related embodiment, the present invention provides an assay device, preferably for
25 use in the diagnosis or prognosis of ovarian cancer, said device comprising a plurality of different antibodies immobilized to a solid phase, wherein each of said antibodies binds to a polypeptide listed in Tables 1-3. Preferably, the solid phase is a substantially planar chip.

Preferably, the assay device *supra* is used in a method of diagnosis or prognosis as
30 described herein.

Alternatively, the assay device is used to identify modulatory compounds of the expression of one or more genes/proteins listed in any one of Tables 1-3.

In a further aspect, the present invention provides a non-human transgenic animal which is transgenic by virtue of comprising a gene set forth in any one of Tables 1-3 and, in particular, to the use of any such transgenic animal in the performance of a diagnostic or prognostic method of the invention as transgenic "knock-out" animals that have disrupted
5 expression of a gene as set forth in any one of Tables 1-3.

In a further aspect, the present invention provides an isolated polynucleotide selected from the group consisting of:

- 10 (a) polynucleotides comprising a nucleotide sequence as shown in Tables 1-3, or the complement thereof;
- (b) polynucleotides comprising a nucleotide sequence capable of selectively hybridizing to a nucleotide sequence as shown in Tables 1-3;
- (c) polynucleotides comprising a nucleotide sequence capable of selectively hybridizing to the complement of a nucleotide sequence as shown in Tables 1-3;
- 15 and
- (d) polynucleotides comprising a polynucleotide sequence which is degenerate as a result of the genetic code to the polynucleotides defined in (a), (b) or (c).

Preferred polynucleotides comprise a polynucleotide sequence as shown in Tables 1-3
20 or a sequence having at least 80% homology thereto.

Preferably, the isolated polynucleotide is used for the diagnosis or prognosis of ovarian cancer, more preferably by a method as described herein. . In a particularly preferred embodiment, the present invention provides for the use of a polynucleotide as set forth in
25 any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

The present invention also provides a nucleic acid vector comprising a polynucleotide of the invention. In one embodiment, the polynucleotide is operably linked to a regulatory
30 control sequence capable of directing expression of the polynucleotide in a host cell. In a particularly preferred embodiment, the present invention provides for the use of a vector comprising a polynucleotide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

The present invention further provides a host cell comprising a vector as described in the preceding paragraph. In a particularly preferred embodiment, the present invention provides for the use of a host cell comprising an introduced polynucleotide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the
5 preparation of a medicament for the treatment of ovarian cancer.

In a further aspect, the present invention provides an isolated polypeptide which is encoded by a gene set forth in any one of Tables 1-3. The present invention also provides an isolated polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence
10 at least 80% identical to a sequence as shown in Tables 1-3. In a particularly preferred embodiment, the present invention provides for the use of an isolated polypeptide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

15 In a further aspect the present invention provides an antibody that binds specifically a polypeptide listed in Tables 1-3. In a particularly preferred embodiment, the present invention provides for the use of an antibody that binds to an isolated polypeptide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

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Brief description of the Drawings

Figure 1 is a photographic representation showing expression of genes as identified by immunohistochemical staining of fixed normal (i.e. non-cancerous or healthy) tissues
25 (panel A) or ovarian cancer tissue (panel B). The inset in panel A shows inclusion cysts. The expression levels of the following genes listed in Table 1 or Table 3 were determined: Claudin-3 (SEQ ID NO: 15); EP-CAM (Accession No. NM_002354); and SOX17 (SEQ ID NO: 17). Positive controls CA125, MUC-1 and E-Cadherin were also included for comparison.

Figure 2 is a graphical representation showing the correlation between expression of different genes in serous ovarian cancer (SOC), mucinous ovarian cancer (MOC), endometroid ovarian cancer (EnOC) and clear cell ovarian cancer (CICA). Genes indicated on the x-axis in each case are as in the legend to Figure 1.

Figure 3 is a copy of a photographic representation showing immunohistochemical staining of ovary tissue from a normal healthy subject (normal ovary), a subject diagnosed with mucinous ovarian cancer (MOC) and a subject diagnosed with serous ovarian cancer (SOC), following staining with probes that are specific for L1-Cadherin (top row), meprin alpha (middle row) or galectin-4 (lower row). Magnification is indicated as 20-40X.

Figure 4a is a copy of a photographic representation showing immunohistochemical staining of samples from a normal healthy subject (normal) or primary serous ovarian tumor (SOC), following staining with probes that are specific for sFRP4 (top row), or SOCS3 (lower row). Magnification is indicated as 20X.

Figure 4b is a copy of a graphical representation showing a Kaplan-Meier survival curve correlating sFRP4 expression to patient survival over the medium term (i.e., from about 12 months to about 48 months) to long term (more than about 48 months), indicating that high expression of sFRP4 is associated with poor survival in patients (n=127) having SOC (p=0.0056).

Detailed description of the preferred embodiments

Ovarian cancer-associated sequences

Ovarian cancer-associated sequences can include both nucleic acid (i.e., "ovarian cancer-associated genes") and protein (i.e., "ovarian cancer-associated proteins").

As used herein, the term "ovarian cancer-associated protein" shall be taken to mean any protein that has an expression pattern correlated to an ovarian cancer, the recurrence of an ovarian cancer or the survival of a subject suffering from ovarian cancer.

Similarly, the term "ovarian cancer-associated gene" shall be taken to mean any nucleic acid encoding an ovarian cancer-associated protein or nucleic acid having an expression profile that is correlated to an ovarian cancer, the recurrence of an ovarian cancer or the survival of a subject suffering from ovarian cancer.

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As will be appreciated by those in the art and is more fully outlined below, ovarian cancer-associated genes are useful in a variety of applications, including diagnostic applications, which will detect naturally occurring nucleic acids, as well as screening applications; e.g., biochips comprising nucleic acid probes or PCR microtitre plates with selected probes to the ovarian cancer sequences are generated.

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For identifying ovarian cancer-associated sequences, the ovarian cancer screen typically includes comparing genes identified in different tissues, e.g., normal and cancerous tissues, or tumour tissue samples from patients who have metastatic disease vs. non metastatic tissue. Other suitable tissue comparisons include comparing ovarian cancer samples with metastatic cancer samples from other cancers, such as lung, breast, gastrointestinal cancers, ovarian, etc. Samples of different stages of ovarian cancer, e.g., survivor tissue, drug resistant states, and tissue undergoing metastasis, are applied to biochips comprising nucleic acid probes. The samples are first microdissected, if applicable, and treated as is known in the art for the preparation of mRNA. Suitable biochips are commercially available, e.g. from Affymetrix. Gene expression profiles as described herein are generated and the data analyzed.

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In one embodiment, the genes showing changes in expression as between normal and disease states are compared to genes expressed in other normal tissues, preferably normal ovarian, but also including, and not limited to lung, heart, brain, liver, breast, kidney, muscle, colon, small intestine, large intestine, spleen, bone and placenta. In a preferred embodiment, those genes identified during the ovarian cancer screen that are expressed in any significant amount in other tissues are removed from the profile, although in some embodiments, this is not necessary. That is, when screening for drugs, it is usually preferable that the target be disease specific, to minimise possible side effects.

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In a preferred embodiment, ovarian cancer-associated sequences are those that are up-regulated in ovarian cancer; that is, the expression of these genes is modified (up-

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regulated or down-regulated) in ovarian cancer tissue as compared to non-cancerous tissue (see Table 1).

"Up-regulation" as used herein means at least about a two-fold change, preferably at least about a three fold change, with at least about five-fold or higher being preferred. All Unigene cluster identification numbers and accession numbers herein are for the GenBank sequence database and the sequences of the accession numbers are hereby expressly incorporated by reference. Sequences are also available in other databases, e.g., European Molecular Biology Laboratory (EMBL) and DNA Database of Japan (DDBJ).

"Down-regulation" as used herein often means at least about a 1.5-fold change more preferably a two-fold change, preferably at least about a three fold change, with at least about five-fold or higher being most preferred.

Particularly preferred sequences are those referred to in Tables 1 or 3 that have a P value of less than 0.05, more preferably a P value of less than about 0.01.

Similarly, preferred sequences are those referred to in Table 2 as having an absolute ratio of expression between ovarian patients and normal patients of at least about ± 5.0 , more preferably at least about ± 6.0 , even more preferably at least about ± 7.0 or at least about ± 8.0 or at least about ± 9.0 or at least about ± 10.0 .

Detection of ovarian cancer sequences for diagnostic/prognostic applications

In one aspect, the RNA expression levels of genes are determined for different cellular states in the ovarian cancer phenotype. Expression levels of genes in normal tissue (i.e., not undergoing ovarian cancer) and in ovarian cancer tissue (and in some cases, for varying severities of ovarian cancer that relate to prognosis, as outlined below) are evaluated to provide expression profiles. An expression profile of a particular cell state or point of development is essentially a "fingerprint" of the state. While two states may have any particular gene similarly expressed, the evaluation of a number of genes simultaneously allows the generation of a gene expression profile that is reflective of the state of the cell. By comparing expression profiles of cells in different states, information regarding which genes are important (including both up- and down-regulation of genes) in each of these states is obtained. Then, diagnosis are performed or confirmed to

determine whether a tissue sample has the gene expression profile of normal or cancerous tissue. This will provide for molecular diagnosis of related conditions.

"Differential expression," or grammatical equivalents as used herein, refers to qualitative or quantitative differences in the temporal and/or cellular gene expression patterns within and among cells and tissue. Thus, a differentially expressed gene can qualitatively have its expression altered, including an activation or inactivation, in, e.g., normal versus ovarian cancer tissue. Genes are turned on or turned off in a particular state, relative to another state thus permitting comparison of two or more states. A qualitatively regulated gene will exhibit an expression pattern within a state or cell type which is detectable by standard techniques. Some genes will be expressed in one state or cell type, but not in both. Alternatively, the difference in expression are quantitative, e.g., in that expression is increased or decreased; i.e., gene expression is either upregulated, resulting in an increased amount of transcript, or downregulated, resulting in a decreased amount of transcript. The degree to which expression differs need only be large enough to quantify via standard characterization techniques as outlined below, such as by use of Affymetrix GeneChipTM expression arrays, Lockhart, *Nature Biotechnology* 14:1675-1680 (1996), hereby expressly incorporated by reference. Other techniques include, but are not limited to, quantitative reverse transcriptase PCR, northern analysis and RNase protection. As outlined above, preferably the change in expression (i.e., upregulation or downregulation) is at least about 50%, more preferably at least about 100%, more preferably at least about 150%, more preferably at least about 200%, with from 300 to at least 1000% being especially preferred.

Evaluation are at the gene transcript, or the protein level. The amount of gene expression are monitored using nucleic acid probes to the DNA or RNA equivalent of the gene transcript, and the quantification of gene expression levels, or, alternatively, the final gene product itself (protein) are monitored, e.g., with antibodies to the ovarian cancer-associated protein and standard immunoassays (ELISAs, etc.) or other techniques, including mass spectroscopy assays, 2D gel electrophoresis assays, etc. Proteins corresponding to ovarian cancer genes, i.e., those identified as being important in a ovarian cancer phenotype, are evaluated in a ovarian cancer diagnostic test.

In a preferred embodiment, gene expression monitoring is performed on a plurality of genes. Multiple protein expression monitoring are performed as well. Similarly, these assays are performed on an individual basis as well.

In this embodiment, the ovarian cancer nucleic acid probes are attached to biochips as outlined herein for the detection and quantification of ovarian cancer sequences in a particular cell. The assays are further described below in the example. PCR techniques
5 are used to provide greater sensitivity.

In a preferred embodiment nucleic acids encoding the ovarian cancer-associated protein are detected. Although DNA or RNA encoding the ovarian cancer-associated protein are detected, of particular interest are methods wherein an mRNA encoding a ovarian
10 cancer-associated protein is detected. Probes to detect mRNA are a nucleotide/deoxynucleotide probe that is complementary to and hybridizes with the mRNA and includes, but is not limited to, oligonucleotides, cDNA or RNA. Probes also should contain a detectable label, as defined herein. In one method the mRNA is detected after immobilizing the nucleic acid to be examined on a solid support such as
15 nylon membranes and hybridizing the probe with the sample. Following washing to remove the non-specifically bound probe, the label is detected. In another method detection of the mRNA is performed in situ. In this method permeabilized cells or tissue samples are contacted with a detectably labeled nucleic acid probe for sufficient time to allow the probe to hybridize with the target mRNA. Following washing to remove the
20 non-specifically bound probe, the label is detected. For example a digoxigenin labeled riboprobe (RNA probe) that is complementary to the mRNA encoding a ovarian cancer-associated protein is detected by binding the digoxigenin with an anti-digoxigenin secondary antibody and developed with nitro blue tetrazolium and 5-bromo-4-chloro-3-indoyl phosphate.

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In a preferred embodiment, various proteins from the three classes of proteins as described herein (secreted, transmembrane or intracellular proteins) are used in diagnostic assays. The ovarian cancer-associated proteins, antibodies, nucleic acids, modified proteins and cells containing ovarian cancer sequences are used in diagnostic
30 assays. This are performed on an individual gene or corresponding polypeptide level. In a preferred embodiment, the expression profiles are used, preferably in conjunction with high throughput screening techniques to allow monitoring for expression profile genes and/or corresponding polypeptides.

35 As described and defined herein, ovarian cancer-associated proteins, including intracellular, transmembrane or secreted proteins, find use as markers of ovarian cancer.

- Detection of these proteins in putative ovarian cancer tissue allows for detection or diagnosis of ovarian cancer. In one embodiment, antibodies are used to detect ovarian cancer-associated proteins. A preferred method separates proteins from a sample by electrophoresis on a gel (typically a denaturing and reducing protein gel, but are another type of gel, including isoelectric focusing gels and the like). Following separation of proteins, the ovarian cancer-associated protein is detected, e.g., by immunoblotting with antibodies raised against the ovarian cancer-associated protein. Methods of immunoblotting are well known to those of ordinary skill in the art.
- 10 In another preferred method, antibodies to the ovarian cancer-associated protein find use in *in situ* imaging techniques, e.g., in histology (e.g., *Methods in Cell Biology: Antibodies in Cell Biology*, volume 37 (Asai, ed. 1993)). In this method cells are contacted with from one to many antibodies to the ovarian cancer-associated protein(s). Following washing to remove non-specific antibody binding, the presence of the antibody or antibodies is
- 15 detected. In one embodiment the antibody is detected by incubating with a secondary antibody that contains a detectable label. In another method the primary antibody to the ovarian cancer-associated proteins) contains a detectable label, e.g. an enzyme marker that can act on a substrate. In another preferred embodiment each one of multiple primary antibodies contains a distinct and detectable label. This method finds particular
- 20 use in simultaneous screening for a plurality of ovarian cancer-associated proteins. As will be appreciated by one of ordinary skill in the art, many other histological imaging techniques are also provided by the invention.
- In a preferred embodiment the label is detected in a fluorometer which has the ability to
- 25 detect and distinguish emissions of different wavelengths. In addition, a fluorescence activated cell sorter (FACS) are used in the method. In another preferred embodiment, antibodies find use in diagnosing ovarian cancer from blood, serum, plasma, stool, and other samples. Such samples, therefore, are useful as samples to be probed or tested for the presence of ovarian cancer-associated proteins. Antibodies are used to detect a
- 30 ovarian cancer-associated protein by previously described immunoassay techniques including ELISA, immunoblotting (western blotting), immunoprecipitation, BIACORE technology and the like. Conversely, the presence of antibodies may indicate an immune response against an endogenous ovarian cancer-associated protein.
- 35 In a preferred embodiment, *in situ* hybridization of labeled ovarian cancer nucleic acid probes to tissue arrays is done. For example, arrays of tissue samples, including ovarian

cancer tissue and/or normal tissue, are made. In situ hybridization (see, e.g., Ausubel, supra) is then performed. When comparing the fingerprints between an individual and a standard, the skilled artisan can make a diagnosis, a prognosis, or a prediction based on the findings. It is further understood that the genes which indicate the diagnosis may differ from those which indicate the prognosis and molecular profiling of the condition of the cells may lead to distinctions between responsive or refractory conditions or are predictive of outcomes.

In a preferred embodiment, the ovarian cancer-associated proteins, antibodies, nucleic acids, modified proteins and cells containing ovarian cancer sequences are used in prognosis assays. As above, gene expression profiles are generated that correlate to ovarian cancer, in terms of long term prognosis. Again, this are done on either a protein or gene level, with the use of genes being preferred. As above, ovarian cancer probes are attached to biochips for the detection and quantification of ovarian cancer sequences in a tissue or patient. The assays proceed as outlined above for diagnosis. PCR method may provide more sensitive and accurate quantification.

Characteristics of ovarian cancer-associated proteins and genes encoding same

Ovarian cancer-associated proteins of the present invention are classified as secreted proteins, transmembrane proteins or intracellular proteins. In one embodiment, the ovarian cancer-associated protein is an intracellular protein. Intracellular proteins are found in the cytoplasm and/or in the nucleus. Intracellular proteins are involved in all aspects of cellular function and replication (including, e.g., signaling pathways); aberrant expression of such proteins often results in unregulated or dysregulated cellular processes (see, e.g., Molecular Biology of the Cell (Alberts, ed., 3rd ed., 1994). For example, many intracellular proteins have enzymatic activity such as protein kinase activity, protein phosphatase activity, protease activity, nucleotide cyclase activity, polymerase activity and the like. Intracellular proteins also serve as docking proteins that are involved in organizing complexes of proteins, or targeting proteins to various subcellular localizations, and are involved in maintaining the structural integrity of organelles.

An increasingly appreciated concept in characterising proteins is the presence in the proteins of one or more motifs for which defined functions have been attributed. In addition to the highly conserved sequences found in the enzymatic domain of proteins, highly conserved sequences have been identified in proteins that are involved in

protein-protein interaction. For example, Src-homology-2 (SH2) domains bind tyrosine-phosphorylated targets in a sequence dependent manner. PTB domains, which are distinct from SH2 domains, also bind tyrosine phosphorylated targets. SH3 domains bind to proline-rich targets. In addition, PH domains, tetratricopeptide repeats and WD domains to name only a few, have been shown to mediate protein-protein interactions. Some of these may also be involved in binding to phospholipids or other second messengers. As will be appreciated by one of ordinary skill in the art, these motifs are identified on the basis of primary sequence; thus, an analysis of the sequence of proteins may provide insight into both the enzymatic potential of the molecule and/or molecules with which the protein may associate. One useful database is Pfam (protein families), which is a large collection of multiple sequence alignments and hidden Markov models covering many common protein domains. Versions are available via the internet from Washington University in St. Louis, the Sanger Center in England, and the Karolinska Institute in Sweden (see, e.g., Bateman et al., 2000, Nuc. Acids Res. 28: 263-266; Sonnhhammer et al., 1997, Proteins 28: 405-420; Bateman et al., 1999, Nuc. Acids Res. 27:260-262; and Sonnhhammer et al., 1998, Nuc. Acids Res. 26: 320-322.

In another embodiment, the ovarian cancer sequences are transmembrane proteins. Transmembrane proteins are molecules that span a phospholipid bilayer of a cell. They may have an intracellular domain, an extracellular domain, or both. The intracellular domains of such proteins may have a number of functions including those already described for intracellular proteins. For example, the intracellular domain may have enzymatic activity and/or may serve as a binding site for additional proteins. Frequently the intracellular domain of transmembrane proteins serves both roles. For example certain receptor tyrosine kinases have both protein kinase activity and SH2 domains. In addition, autophosphorylation of tyrosines on the receptor molecule itself, creates binding sites for additional SH2 domain containing proteins.

Transmembrane proteins may contain from one to many transmembrane domains. For example, receptor tyrosine kinases, certain cytokine receptors, receptor guanylyl cyclases and receptor serine/threonine protein kinases contain a single transmembrane domain. However, various other proteins including channels and adenylyl cyclases contain numerous transmembrane domains. Many important cell surface receptors such as G protein coupled receptors (GPCRs) are classified as "seven transmembrane domain" proteins, as they contain 7 membrane spanning regions. Characteristics of transmembrane domains include approximately 20 consecutive hydrophobic amino acids

- that are followed by charged amino acids. Therefore, upon analysis of the amino acid sequence of a particular protein, the localization and number of transmembrane domains within the protein are predicted (see, e.g. PSORT web site <http://psort.nibb.ac.jp/>). Important transmembrane protein receptors include, but are not limited to the insulin receptor, insulin-like growth factor receptor, human growth hormone receptor, glucose transporters, transferrin receptor, epidermal growth factor receptor, low density lipoprotein receptor, epidermal growth factor receptor, leptin receptor, interleukin receptors, e.g. IL-1 receptor, IL-2 receptor,
- 10 The extracellular domains of transmembrane proteins are diverse; however, conserved motifs are found repeatedly among various extracellular domains. Conserved structure and/or functions have been ascribed to different extracellular motifs. Many extracellular domains are involved in binding to other molecules. In one aspect, extracellular domains are found on receptors. Factors that bind the receptor domain include circulating ligands,
- 15 which are peptides, proteins, or small molecules such as adenosine and the like. For example, growth factors such as EGF, FGF and PDGF are circulating growth factors that bind to their cognate receptors to initiate a variety of cellular responses. Other factors include cytokines, mitogenic factors, neurotrophic factors and the like. Extracellular domains also bind to cell-associated molecules. In this respect, they mediate cell-cell
- 20 interactions., Cell-associated ligands are tethered to the cell, e.g., via a glycosylphosphatidylinositol (GPI) anchor, or may themselves be transmembrane proteins. Extracellular domains also associate with the extracellular matrix and contribute to the maintenance of the cell structure.
- 25 Ovarian cancer-associated proteins that are transmembrane are particularly preferred in the present invention as they are readily accessible targets for immunotherapeutics, as are described herein. In addition, as outlined below, transmembrane proteins are also useful in imaging modalities. Antibodies are used to label such readily accessible proteins *in situ*. Alternatively, antibodies can also label intracellular proteins, in which
- 30 case samples are typically permeabilized to provide access to intracellular proteins.

It will also be appreciated by those in the art that a transmembrane protein are made soluble by removing transmembrane sequences, e.g., through recombinant methods. Furthermore, transmembrane proteins that have been made soluble are made to be

35 secreted through recombinant means by adding an appropriate signal sequence.

In another embodiment, the ovarian cancer-associated proteins are secreted proteins; the secretion of which are either constitutive or regulated. These proteins have a signal peptide or signal sequence that targets the molecule to the secretory pathway. Secreted proteins are involved in numerous physiological events; by virtue of their circulating nature, they serve to transmit signals to various other cell types. The secreted protein may function in an autocrine manner (acting on the cell that secreted the factor), a paracrine manner (acting on cells in close proximity to the cell that secreted the factor) or an endocrine manner (acting on cells at a distance). Thus secreted molecules find use in modulating or altering numerous aspects of physiology. Ovarian cancer-associated proteins that are secreted proteins are particularly preferred in the present invention as they serve as good targets for diagnostic markers, e.g., for blood, plasma, serum, or stool tests.

Mammalian subjects

The present invention provides nucleic acid and protein sequences that are differentially expressed in ovarian cancer, herein termed "ovarian cancer sequences." As outlined below, ovarian cancer sequences include those that are up-regulated (i.e., expressed at a higher level) in ovarian cancer, as well as those that are down-regulated (i.e., expressed at a lower level). In a preferred embodiment, the ovarian cancer sequences are from humans; however, as will be appreciated by those in the art, ovarian cancer sequences from other organisms are useful in animal models of disease and drug evaluation; thus, other ovarian cancer sequences are provided, from vertebrates, including mammals, including rodents (rats, mice, hamsters, guinea pigs, etc.), primates, farm animals (including sheep, goats, pigs, cows, horses, etc.) and pets, e.g., (dogs, cats, etc.).

Assay control samples

It will be apparent from the preceding discussion that many of the diagnostic methods provided by the present invention involve a degree of quantification to determine, on the one hand, the over-expression or reduced-expression of a diagnostic/prognostic marker in tissue that is suspected of comprising a cancer cell. Such quantification can be readily provided by the inclusion of appropriate control samples in the assays described below, derived from healthy or normal individuals. Alternatively, if internal controls are not included in each assay conducted, the control may be derived from an established data set that has been generated from healthy or normal individuals.

In the present context, the term "healthy individual" shall be taken to mean an individual who is known not to suffer from ovarian cancer, such knowledge being derived from clinical data on the individual, including, but not limited to, a different cancer assay to that described herein. As the present invention is particularly useful for the early detection of ovarian cancer, it is preferred that the healthy individual is asymptomatic with respect to the early symptoms associated with ovarian cancer. Although early detection using well-known procedures is difficult, reduced urinary frequency, rectal pressure, and abdominal bloating and swelling, are associated with the disease in its early stages, and, as a consequence, healthy individuals should not have any of these clinical symptoms. Clearly, subjects suffering from later symptoms associated with ovarian cancer, such as, for example, metastases in the omentum, abdominal fluid, lymph nodes, lung, liver, brain, or bone, and subjects suffering from spinal cord compression, elevated calcium level, chronic pain, or pleural effusion, should also be avoided from the "healthy individual" data set.

The term "normal individual" shall be taken to mean an individual having a normal level of expression of a cancer-associate gene or cancer-associated protein in a particular sample derived from said individual. As will be known to those skilled in the art, data obtained from a sufficiently large sample of the population will normalize, allowing the generation of a data set for determining the average level of a particular parameter. Accordingly, the level of expression of a cancer-associate gene or cancer-associated protein can be determined for any population of individuals, and for any sample derived from said individual, for subsequent comparison to levels determined for a sample being assayed. Where such normalized data sets are relied upon, internal controls are preferably included in each assay conducted to control for variation.

In one embodiment, the present invention provides a method for detecting a cancer cell in a subject, said method comprising:

- (i) determining the level of mRNA encoding a cancer-associated protein expressed in a test sample from said subject; and
- (ii) comparing the level of mRNA determined at (i) to the level of mRNA encoding a cancer-associated protein expressed in a comparable sample from a healthy or normal individual,

wherein a level of mRNA at (i) that is modified in the test sample relative to the comparable sample from the normal or healthy individual is indicative of the presence of a cancer cell in said subject.

Alternatively, or in addition, the control may comprise a cancer-associated sequence that is known to be expressed at a particular level in an ovarian cancer, eg., CA125, MUC-1 or E-Cadherin, amongst others.

5

Biological samples

Preferred biological samples in which the assays of the invention are performed include bodily fluids, ovarian tissue and cells, and those tissues known to comprise cancer cells arising from a metastasis of an ovarian cancer, such as, for example, in carcinomas of
10 the lung, prostate, breast, colon, pancreas, placenta, or omentum, and in cells of brain anaplastic oligodendrogliomas.

Bodily fluids shall be taken to include whole blood, serum, peripheral blood mononuclear cells (PBMC), or buffy coat fraction.

15

In the present context, the term "cancer cell" includes any biological specimen or sample comprising a cancer cell irrespective of its degree of isolation or purity, such as, for example, tissues, organs, cell lines, bodily fluids, or histology specimens that comprise a cell in the early stages of transformation or having been transformed.

20

As the present invention is particularly useful for the early detection and prognosis of cancer of the medium to long term, the definition of "cancer cell" is not to be limited by the stage of a cancer in the subject from which said cancer cell is derived (ie. whether or not the patient is in remission or undergoing disease recurrence or whether or not the
25 cancer is a primary tumor or the consequence of metastases). Nor is the term "cancer cell" to be limited by the stage of the cell cycle of said cancer cell.

Preferably, the sample comprises ovarian tissue, prostate tissue, kidney tissue, uterine tissue, placenta, a cervical specimen, omentum, rectal tissue, brain tissue, bone tissue,
30 lung tissue, lymphatic tissue, urine, semen, blood, abdominal fluid, or serum, or a cell preparation or nucleic acid preparation derived therefrom. More preferably, the sample comprises serum or abdominal fluid, or a tissue selected from the group consisting of: ovary, lymph, lung, liver, brain, placenta, brain, omentum, and prostate. Even more preferably, the sample comprises serum or abdominal fluid, ovary (eg. OSE), or lymph
35 node tissue. The sample can be prepared on a solid matrix for histological analyses, or alternatively, in a suitable solution such as, for example, an extraction buffer or

suspension buffer, and the present invention clearly extends to the testing of biological solutions thus prepared.

Polynucleotide probes and amplification primers

- 5 Polynucleotide probes are derived from or comprise the nucleic acid sequences whose nucleotide sequences are provided by reference to the public database accession numbers given in Tables 1-3 (referred to herein as the nucleotide sequences shown in Tables 1-3), and sequences homologues thereto as well as variants, derivatives and fragments thereof.

10

Whilst the probes may comprise double-stranded or single-stranded nucleic acid, single-stranded probes are preferred because they do not require melting prior to use in hybridizations. On the other hand, longer probes are also preferred because they can be used at higher hybridization stringency than shorter probes and may produce lower background hybridization than shorter probes.

15

- So far as shorter probes are concerned, single-stranded, chemically-synthesized oligonucleotide probes are particularly preferred by the present invention. To reduce the noise associated with the use of such probes during hybridization, the nucleotide sequence of the probe is carefully selected to maximize the T_m at which hybridizations can be performed, reduce non-specific hybridization, and to reduce self-hybridization. Such considerations may be particularly important for applications involving high throughput screening using microarray technology. In general, this means that the nucleotide sequence of an oligonucleotide probe is selected such that it is unique to the target RNA or protein-encoding sequence, has a low propensity to form secondary structure, low self-complementary, and is not highly A/T-rich.

20

25

- The only requirement for the probes is that they cross-hybridize to nucleic acid encoding the target diagnostic protein or the complementary nucleotide sequence thereto and are sufficiently unique in sequence to generate high signal:noise ratios under specified hybridization conditions. As will be known to those skilled in the art, long nucleic acid probes are preferred because they tend to generate higher signal:noise ratios than shorter probes and/or the duplexes formed between longer molecules have higher melting temperatures (i.e. T_m values) than duplexes involving short probes. Accordingly, full-length DNA or RNA probes are contemplated by the present invention, as are specific probes comprising the sequence of the 3'-untranslated region or complementary thereto.

30

35

In a particularly preferred embodiment, the nucleotide sequence of an oligonucleotide probe has no detectable nucleotide sequence identity to a nucleotide sequence in a BLAST search (Altschul *et al.*, *J. Mol. Biol.* 215, 403-410, 1990) or other database search, other than a sequence selected from the group consisting of: (a) a sequence encoding a polypeptide listed in any one of Tables 1-3; (b) the 5'-untranslated region of a sequence encoding a polypeptide listed in any one of Tables 1-3; (c) a 3'-untranslated region of a sequence encoding a polypeptide listed in any one of Tables 1-3; and (d) an exon region of a sequence encoding a polypeptide listed in any one of Tables 1-3.

Additionally, the self-complementarity of a nucleotide sequence can be determined by aligning the sequence with its reverse complement, wherein detectable regions of identity are indicative of potential self-complementarity. As will be known to those skilled in the art, such sequences may not necessarily form secondary structures during hybridization reaction, and, as a consequence, successfully identify a target nucleotide sequence. It is also known to those skilled in the art that, even where a sequence does form secondary structures during hybridization reactions, reaction conditions can be modified to reduce the adverse consequences of such structure formation. Accordingly, a potential for self-complementarity should not necessarily exclude a particular candidate oligonucleotide from selection. In cases where it is difficult to determine nucleotide sequences having no potential self-complementarity, the uniqueness of the sequence should outweigh a consideration of its potential for secondary structure formation.

Recommended pre-requisites for selecting oligonucleotide probes, particularly with respect to probes suitable for microarray technology, are described in detail by Lockhart *et al.*, "Expression monitoring by hybridization to high-density oligonucleotide arrays", *Nature Biotech.* 14, 1675-1680, 1996.

The nucleic acid probe may comprise a nucleotide sequence that is within the coding strand of a gene listed in any one of Tables 1-3. Such "sense" probes are useful for detecting RNA by amplification procedures, such as, for example, polymerase chain reaction (PCR), and more preferably, quantitative PCR or reverse transcription polymerase chain reaction (RT-PCR). Alternatively, "sense" probes may be expressed to produce polypeptides or immunologically active derivatives thereof that are useful for detecting the expressed protein in samples.

- The nucleotide sequences referred to in Tables 1-3 and homologues thereof, typically encode polypeptides. It will be understood by a skilled person that numerous different polynucleotides can encode the same polypeptide as a result of the degeneracy of the genetic code. In addition, it is to be understood that skilled persons may, using routine techniques, make nucleotide substitutions that do not affect the polypeptide sequence encoded by the polynucleotides of the invention to reflect the codon usage of any particular host organism in which the polypeptides of the invention are to be expressed.
- 10 Polynucleotides may comprise DNA or RNA. They are single-stranded or double-stranded. They may also be polynucleotides which include within them synthetic or modified nucleotides. A number of different types of modification to oligonucleotides are known in the art. These include methylphosphonate and phosphorothioate backbones, addition of acridine or polylysine chains at the 3' and/or 5' ends of the molecule. For the purposes of the present invention, it is to be understood that the polynucleotides described herein are modified by any method available in the art. Such modifications are carried out in order to enhance the *in vivo* activity or life span of the diagnostic/prognostic polynucleotides.
- 15
- 20 The terms "variant" or "derivative" in relation to the nucleotide sequences of the present invention include any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) nucleic acid from or to the sequence provided that the resultant nucleotide sequence codes for a polypeptide having biological activity, preferably having substantially the same activity as the polypeptide sequences presented in the sequence listings.
- 25

With respect to sequence homology, preferably there is at least 75%, more preferably at least 85%, more preferably at least 90% homology to a sequence shown in Tables 1-3 herein over a region of at least 20, preferably at least 25 or 30, for instance at least 40, 60, 100, 500, 1000 or more contiguous nucleotides. More preferably there is at least 95%, more preferably at least 98%, homology. In one embodiment, homologues are naturally occurring sequences, such as orthologues, tissue-specific isoforms and allelic variants.

Homology comparisons are conducted by eye, or more usually, with the aid of readily available sequence comparison programs. These commercially available computer programs can calculate % homology between two or more sequences.

35

Percentage (%) homology are calculated over contiguous sequences, i.e. one sequence is aligned with the other sequence and each nucleotide in one sequence directly compared with the corresponding nucleotide in the other sequence, one base at a time. This is called
5 an "ungapped" alignment. Typically, such ungapped alignments are performed only over a relatively short number of bases (for example less than 50 contiguous nucleotides).

Although this is a very simple and consistent method, it fails to take into consideration that, for example, in an otherwise identical pair of sequences, one insertion or deletion will cause
10 the following nucleotides to be put out of alignment, thus potentially resulting in a large reduction in % homology when a global alignment is performed. Consequently, most sequence comparison methods are designed to produce optimal alignments that take into consideration possible insertions and deletions without penalising unduly the overall homology score. This is achieved by inserting "gaps" in the sequence alignment to try to
15 maximise local homology.

However, these more complex methods assign "gap penalties" to each gap that occurs in the alignment so that, for the same number of identical amino acids, a sequence alignment with as few gaps as possible - reflecting higher relatedness between the two compared
20 sequences - will achieve a higher score than one with many gaps. "Affine gap costs" are typically used that charge a relatively high cost for the existence of a gap and a smaller penalty for each subsequent residue in the gap. This is the most commonly used gap scoring system. High gap penalties will of course produce optimised alignments with fewer gaps. Most alignment programs allow the gap penalties to be modified. However, it is
25 preferred to use the default values when using such software for sequence comparisons.

In determining whether or not two amino acid sequences fall within the stated defined percentage identity limits, those skilled in the art will be aware that it is necessary to conduct a side-by-side comparison of amino acid sequences. In such comparisons or
30 alignments, differences will arise in the positioning of non-identical amino acid residues depending upon the algorithm used to perform the alignment. In the present context, references to percentage identities and similarities between two or more amino acid sequences shall be taken to refer to the number of identical and similar residues respectively, between said sequences as determined using any standard algorithm
35 known to those skilled in the art. In particular, amino acid identities and similarities are calculated using the GAP program of the Computer Genetics Group, Inc., University

Research Park, Madison, Wisconsin, United States of America (Devereaux *et al.*, *Nucl. Acids Res.* 12, 387-395, 1984), which utilizes the algorithm of Needleman and Wunsch *J. Mol. Biol.* 48, 443-453, 1970, or alternatively, the CLUSTAL W algorithm of Thompson *et al.*, *Nucl. Acids Res.* 22, 4673-4680, 1994, for multiple alignments, to maximize the
5 number of identical/similar amino acids and to minimize the number and/or length of sequence gaps in the alignment.

A suitable computer program for carrying out such an alignment is the GCG Wisconsin Bestfit package (University of Wisconsin, U.S.A.; Devereux *et al.*, 1984, *Nucleic Acids Research* 12:387). The default scoring matrix has a match value of 10 for each identical
10 nucleotide and -9 for each mismatch. The default gap creation penalty is -50 and the default gap extension penalty is -3 for each nucleotide.

Examples of other software than can perform sequence comparisons include, but are not
15 limited to, the BLAST package (see Ausubel *et al.*, 1999 *ibid* – Chapter 18), FASTA (Atschul *et al.*, 1990, *J. Mol. Biol.*, 403-410) and the GENEWORKS suite of comparison tools. Both BLAST and FASTA are available for offline and online searching (see Ausubel *et al.*, 1999 *ibid*, pages 7-58 to 7-60). However it is preferred to use the GCG Bestfit program.

20 Once the software has produced an optimal alignment, it is possible to calculate % homology, preferably % sequence identity. The software typically does this as part of the sequence comparison and generates a numerical result.

25 A preferred sequence comparison program is the GCG Wisconsin Bestfit program described above.

The present invention also encompasses the use of nucleotide sequences that are capable of hybridizing selectively to the sequences presented herein, or any variant, fragment or
30 derivative thereof, or to the complement of any of the above. Nucleotide sequences are preferably at least 15 nucleotides in length, more preferably at least 20, 30, 40 or 50 nucleotides in length.

The term "hybridization" as used herein shall include "the process by which a strand of
35 nucleic acid joins with a complementary strand through base pairing" as well as the process of amplification as carried out in polymerase chain reaction technologies.

Polynucleotides capable of selectively hybridizing to the nucleotide sequences presented herein, or to their complement, will be generally at least 70%, preferably at least 80 or 90% and more preferably at least 95% or 98% homologous to the corresponding nucleotide
5 sequences referred to in Tables 1-3 over a region of at least 20, preferably at least 25 or 30, for instance at least 40, 60, 100, 500, 1000 or more contiguous nucleotides.

The term "selectively hybridizable" means that the polynucleotide used as a probe is used under conditions where a target polynucleotide is found to hybridize to the probe at a level
10 significantly above background. The background hybridization may occur because of other polynucleotides present, for example, in the cDNA or genomic DNA library being screening. In this event, background implies a level of signal generated by interaction between the probe and a non-specific DNA member of the library which is less than 10 fold, preferably less than 100 fold as intense as the specific interaction observed with the target DNA. The
15 intensity of interaction are measured, for example, by radiolabelling the probe, e.g. with ³²P.

Hybridization conditions are based on the melting temperature (T_m) of the nucleic acid binding complex, as taught in Berger and Kimmel (1987, Guide to Molecular Cloning Techniques, Methods in Enzymology, Vol 152, Academic Press, San Diego CA), and
20 confer a defined "stringency" as explained below.

For the purposes of defining the level of stringency, a high stringency hybridization is achieved using a hybridization buffer and/or a wash solution comprising the following:

- (i) a salt concentration that is equivalent to 0.1xSSC-0.2xSSC buffer or lower salt
25 concentration;
- (ii) a detergent concentration equivalent to 0.1% (w/v) SDS or higher; and
- (iii) an incubation temperature of 55°C or higher.

Conditions for specifically hybridizing nucleic acid, and conditions for washing to remove
30 non-specific hybridizing nucleic acid, are well understood by those skilled in the art. For the purposes of further clarification only, reference to the parameters affecting hybridization between nucleic acid molecules is found in Ausubel *et al.* (Current Protocols in Molecular Biology, Wiley Interscience, ISBN 047150338, 1992), which is herein incorporated by reference.

Maximum stringency typically occurs at about $T_m - 5^\circ\text{C}$ (5°C below the T_m of the probe); high stringency at about 5°C to 10°C below T_m ; intermediate stringency at about 10°C to 20°C below T_m ; and low stringency at about 20°C to 25°C below T_m . As will be understood by those of skill in the art, a maximum stringency hybridization are used to
5 identify or detect identical polynucleotide sequences while an intermediate (or low) stringency hybridization are used to identify or detect similar or related polynucleotide sequences.

In a preferred aspect, the present invention covers nucleotide sequences that can hybridize
10 to the nucleotide sequence of the present invention under stringent conditions (e.g. 65°C and $0.1\times\text{SSC}$ { $1\times\text{SSC} = 0.15\text{ M NaCl}$, $0.015\text{ M Na}_3\text{Citrate pH } 7.0$ }).

Where the diagnostic/prognostic polynucleotide is double-stranded, both strands of the duplex, either individually or in combination, are encompassed by the present invention.
15 Where the polynucleotide is single-stranded, it is to be understood that the complementary sequence of that polynucleotide is also included within the scope of the present invention.

Polynucleotides which are not 100% homologous to the sequences of the present invention but are useful in performing the diagnostic and/or prognostic assays of the invention by
20 virtue of their ability to selectively hybridize to the target gene transcript, or to encode an immunologically cross-reactive protein to the target protein, are obtained in a number of ways, such as, for example by probing DNA libraries made from a range of individuals, for example individuals from different populations. In particular, given that that changes in the expression of diagnostic/prognostic cancer-associated genes correlate with ovarian cancer,
25 characterisation of variant sequences in individuals suffering from ovarian cancer is used to identify variations in the sequences of ovarian-cancer associated genes (and proteins) that are predictive of and/or causative of ovarian cancer.

Accordingly the present invention provides methods of identifying sequence variants that
30 are associated with ovarian cancer which methods comprise determining all or part of the nucleotide sequence of a gene referred to in Tables 1-3, derived from an individual suffering from ovarian cancer and comparing the sequence to that of the corresponding wild-type gene.

35 In addition, other viral/bacterial, or cellular homologues particularly cellular homologues found in mammalian cells (e.g. rat, mouse, bovine and primate cells), are obtained and such

homologues and fragments thereof in general will be capable of selectively hybridizing to the sequences shown in the sequence listing herein. Such sequences are obtained by probing cDNA libraries made from or genomic DNA libraries from other animal species, and probing such libraries with probes comprising all or part of the sequences referred to in
5 Tables 1-3 under conditions of medium to high stringency. Similar considerations apply to obtaining species homologues and allelic variants of the nucleotide sequences referred to in Tables 1-3.

10 Variants and strain/species homologues may also be obtained using degenerate PCR which will use primers designed to target sequences within the variants and homologues encoding conserved amino acid sequences within the sequences of the present invention. Conserved sequences are predicted, for example, by aligning the amino acid sequences from several variants/homologues. Sequence alignments are performed using computer software known in the art. For example the GCG Wisconsin PileUp program is widely used.

15

The primers used in degenerate PCR will contain one or more degenerate positions and will be used at stringency conditions lower than those used for cloning sequences with single sequence primers against known sequences.

20 Alternatively, such polynucleotides are obtained by site-directed mutagenesis of characterised sequences, such as the sequences referred to in Tables 1-3. This are useful where for example silent codon changes are required to sequences to optimise codon preferences for a particular host cell in which the polynucleotide sequences are being expressed. Other sequence changes are desired in order to introduce restriction enzyme
25 recognition sites, or to alter the property or function of the polypeptides encoded by the polynucleotides.

Polynucleotides comprising a diagnostic/prognostic cancer-associated gene are used to produce a primer by standard derivatization means, e.g. a PCR primer, a primer for an
30 alternative amplification reaction, a probe e.g. labelled with a detectable label by conventional means using radioactive or non-radioactive labels, or the polynucleotides are cloned into vectors. Such primers, probes and other fragments will be at least 15, preferably at least 20, for example at least 25, 30 or 40 nucleotides in length. Preferred fragments are less than 5000, 2000, 1000, 500 or 200 nucleotides in length.

35

Polynucleotides such as a DNA polynucleotides and probes according to the invention are produced by recombinant or synthetic means, including cloning by standard techniques.

5 In general, primers will be produced by synthetic means, involving a step wise manufacture of the desired nucleic acid sequence one nucleotide at a time. Techniques for accomplishing this using automated techniques are readily available in the art.

10 Longer polynucleotides will generally be produced using recombinant means, for example using PCR (polymerase chain reaction) cloning techniques. This will involve making a pair of primers (e.g. of about 15 to 30 nucleotides) flanking a region of the sequence which it is desired to clone, bringing the primers into contact with mRNA or cDNA obtained from an animal or human cell, performing a polymerase chain reaction under conditions which bring about amplification of the desired region, isolating the amplified fragment (e.g. by purifying the reaction mixture on an agarose gel) and recovering the amplified DNA. The primers are
15 designed to contain suitable restriction enzyme recognition sites so that the amplified DNA are cloned into a suitable cloning vector

Polynucleotide probes or primers preferably carry a detectable label. Suitable labels include radioisotopes such as ^{32}P or ^{35}S , enzyme labels, or other protein labels such as
20 biotin. Such labels are added to polynucleotides or primers and are detected using by techniques known in the art.

Polynucleotide probes or primers labeled or unlabeled are also used by a person skilled in the art in nucleic acid-based tests for detecting or sequencing diagnostic/prognostic
25 cancer-associated gene.

Such tests for detecting generally comprise bringing a biological sample containing DNA or RNA into contact with a probe comprising a polynucleotide probe or primer under at least low stringency hybridization conditions and detecting any duplex formed between
30 the probe/primer and nucleic acid in the sample. Such detection are achieved using techniques such as PCR or by immobilising the probe on a solid support, removing nucleic acid in the sample which is not hybridized to the probe, and then detecting nucleic acid which has hybridized to the probe. Alternatively, the sample nucleic acid are immobilised on a solid support, and the amount of probe bound to such a support are
35 detected. Suitable assay methods of this and other formats are found in for example W089/03891 and W090/13667.

Tests for sequencing nucleotides include bringing a biological sample containing target DNA or RNA into contact with a probe comprising a polynucleotide probe or primer under at least low stringency hybridization conditions and determining the sequence by, for example the Sanger dideoxy chain termination method (see Sambrook et al.).

Such a method generally comprises elongating, in the presence of suitable reagents, the primer by synthesis of a strand complementary to the target DNA or RNA and selectively terminating the elongation reaction at one or more of an A, C, G or T/U residue; allowing strand elongation and termination reaction to occur; separating out according to size the elongated products to determine the sequence of the nucleotides at which selective termination has occurred. Suitable reagents include a DNA polymerase enzyme, the deoxynucleotides dATP, dCTP, dGTP and dTTP, a buffer and ATP. Dideoxynucleotides are used for selective termination.

Tests for detecting or sequencing nucleotides in a biological sample are used as part of the methods of the invention for detecting ovarian cancer-associated transcripts and monitoring the efficacy of treatment of patients suffering from ovarian cancer as described in more detail herein.

The probes/primers may conveniently be packaged in the form of a test kit in a suitable container. In such kits the probe are bound to a solid support where the assay format for which the kit is designed requires such binding. The kit may also contain suitable reagents for treating the sample to be probed, hybridizing the probe to nucleic acid in the sample, control reagents, instructions, and the like.

Preferably, a kit of the invention comprises primers/probes suitable for selectively detecting a plurality of sequences, more preferably for selectively detecting a plurality of sequences that are listed in one or more of Tables 1-3 as having a P value of less than 0.05, more preferably a P value of less than 0.01. Similarly, a kit of the invention preferably comprises primers suitable for selectively detecting a plurality of sequences referred to in Table 1 or 2 or 3.

Nucleic acid-based assay formats

As discussed in detail below, the status of expression of a cancer-associated gene in patient samples may be analyzed by a variety protocols that are well known in the art

including *in situ* hybridization, northern blotting techniques, RT-PCR analysis (such as, for example, performed on laser capture microdissected samples), and microarray technology, such as, for example, using tissue microarrays probed with nucleic acid probes, or nucleic acid microarrays (ie. RNA microarrays or amplified DNA microarrays) microarrays probed with nucleic acid probes. All such assay formats are encompassed by the present invention.

For high throughput screening of large numbers of samples, such as, for example, public health screening of subjects, particularly human subjects, having a higher risk of developing cancer, microarray technology is a preferred assay format.

In accordance with such high throughput formats, techniques for producing immobilised arrays of DNA molecules have been described in the art. Generally, most prior art methods describe how to synthesise single-stranded nucleic acid molecule arrays, using for example masking techniques to build up various permutations of sequences at the various discrete positions on the solid substrate. U.S. Patent No. 5,837,832, the contents of which are incorporated herein by reference, describes an improved method for producing DNA arrays immobilised to silicon substrates based on very large scale integration technology. In particular, U.S. Patent No. 5,837,832 describes a strategy called "tiling" to synthesize specific sets of probes at spatially-defined locations on a substrate which are used to produced the immobilised DNA arrays. U.S. Patent No. 5,837,832 also provides references for earlier techniques that may also be used.

Thus DNA are synthesised *in situ* on the surface of the substrate. However, DNA may also be printed directly onto the substrate using for example robotic devices equipped with either pins or piezo electric devices.

The plurality of polynucleotide sequences are typically immobilised onto or in discrete regions of a solid substrate. The substrate are porous to allow immobilisation within the substrate or substantially non-porous, in which case the library sequences are typically immobilised on the surface of the substrate. The solid substrate are made of any material to which polypeptides can bind, either directly or indirectly. Examples of suitable solid substrates include flat glass, silicon wafers, mica, ceramics and organic polymers such as plastics, including polystyrene and polymethacrylate. It may also be possible to use semi-permeable membranes such as nitrocellulose or nylon membranes, which are widely available. The semi-permeable membranes are mounted on a more robust solid

surface such as glass. The surfaces may optionally be coated with a layer of metal, such as gold, platinum or other transition metal. A particular example of a suitable solid substrate is the commercially available BIAcore™ chip (Pharmacia Biosensors).

- 5 Preferably, the solid substrate is generally a material having a rigid or semi-rigid surface. In preferred embodiments, at least one surface of the substrate will be substantially flat, although in some embodiments it is desirable to physically separate synthesis regions for different polymers with, for example, raised regions or etched trenches. It is also preferred that the solid substrate is suitable for the high density application of DNA
10 sequences in discrete areas of typically from 50 to 100 μm , giving a density of 10000 to 40000 cm^{-2} .

- The solid substrate is conveniently divided up into sections. This is achieved by techniques such as photoetching, or by the application of hydrophobic inks, for example
15 teflon-based inks (Cel-line, USA).

Discrete positions, in which each different member of the array is located may have any convenient shape, e.g., circular, rectangular, elliptical, wedge-shaped, etc.

- 20 Attachment of the polynucleotide sequences to the substrate are by covalent or non-covalent means. The plurality of polynucleotide sequences are attached to the substrate via a layer of molecules to which the sequences bind. For example, the sequences are labelled with biotin and the substrate coated with avidin and/or streptavidin. A convenient feature of using biotinylated sequences is that the efficiency of coupling to the
25 solid substrate are determined easily. Since the library sequences may bind only poorly to some solid substrates, it is often necessary to provide a chemical interface between the solid substrate (such as in the case of glass) and the sequences. Examples of suitable chemical interfaces include hexaethylene glycol. Another example is the use of polylysine coated glass, the polylysine then being chemically modified using standard
30 procedures to introduce an affinity ligand. Other methods for attaching molecules to the surfaces of solid substrate by the use of coupling agents are known in the art, see for example WO98/49557.

- The complete DNA array is typically read at the same time by charged coupled device
35 (CCD) camera or confocal imaging system. Alternatively, the DNA array are placed for detection in a suitable apparatus that can move in an x-y direction, such as a plate

reader. In this way, the change in characteristics for each discrete position are measured automatically by computer controlled movement of the array to place each discrete element in turn in line with the detection means.

- 5 The detection means are capable of interrogating each position in the library array optically or electrically. Examples of suitable detection means include CCD cameras or confocal imaging systems.

- 10 In a preferred embodiment, the level of expression of the cancer-associated gene in the test sample is determined by hybridizing a probe/primer to RNA in the test sample under at least low stringency hybridization conditions and detecting the hybridization using a detection means.

- 15 Similarly, the level of mRNA in the comparable sample from the healthy or normal individual is preferably determined by hybridizing a probe/primer to RNA in said comparable sample under at least low stringency hybridization conditions and detecting the hybridization using a detection means.

- 20 For the purposes of defining the level of stringency to be used in these diagnostic assays, a low stringency is defined herein as being a hybridization and/or a wash carried out in 6xSSC buffer, 0.1% (w/v) SDS at 28°C, or equivalent conditions. A moderate stringency is defined herein as being a hybridization and/or washing carried out in 2xSSC buffer, 0.1% (w/v) SDS at a temperature in the range 45°C to 65°C, or equivalent conditions. A high stringency is defined herein as being a hybridization and/or wash
25 carried out in 0.1xSSC buffer, 0.1% (w/v) SDS, or lower salt concentration, and at a temperature of at least 65°C, or equivalent conditions. Reference herein to a particular level of stringency encompasses equivalent conditions using wash/hybridization solutions other than SSC known to those skilled in the art.

- 30 Generally, the stringency is increased by reducing the concentration of SSC buffer, and/or increasing the concentration of SDS and/or increasing the temperature of the hybridization and/or wash. Those skilled in the art will be aware that the conditions for hybridization and/or wash may vary depending upon the nature of the hybridization matrix used to support the sample RNA, or the type of hybridization probe used.

In general, the sample or the probe is immobilized on a solid matrix or surface (e.g., nitrocellulose). For high throughput screening, the sample or probe will generally comprise an array of nucleic acids on glass or other solid matrix, such as, for example, as described in WO 96/17958. Techniques for producing high density arrays are described, for example, by Fodor *et al.*, Science 767-773, 1991, and in U.S. Pat. No. 5,143,854. Typical protocols for other assay formats can be found, for example in Current Protocols In Molecular Biology, Unit 2 (Northern Blotting), Unit 4 (Southern Blotting), and Unit 18 (PCR Analysis), Frederick M. Ausubul *et al.* (ed), 1995.

10 The detection means according to this aspect of the invention may be any nucleic acid-based detection means such as, for example, nucleic acid hybridization or amplification reaction (eg. PCR), a nucleic acid sequence-based amplification (NASBA) system, inverse polymerase chain reaction (iPCR), *in situ* polymerase chain reaction, or reverse transcription polymerase chain reaction (RT-PCR), amongst others.

15 The probe can be labelled with a reporter molecule capable of producing an identifiable signal (e.g., a radioisotope such as ^{32}P or ^{35}S , or a fluorescent or biotinylated molecule). According to this embodiment, those skilled in the art will be aware that the detection of said reporter molecule provides for identification of the probe and that, following the
20 hybridization reaction, the detection of the corresponding nucleotide sequences in the sample is facilitated. Additional probes can be used to confirm the assay results obtained using a single probe.

Wherein the detection means is an amplification reaction such as, for example, a
25 polymerase chain reaction or a nucleic acid sequence-based amplification (NASBA) system or a variant thereof, one or more nucleic acid probes molecules of at least about 20 contiguous nucleotides in length is hybridized to mRNA encoding a cancer-associated protein, or alternatively, hybridized to cDNA or cRNA produced from said mRNA, and nucleic acid copies of the template are enzymically-amplified.

30 Those skilled in the art will be aware that there must be a sufficiently high percentage of nucleotide sequence identity between the probes and the RNA sequences in the sample template molecule for hybridization to occur. As stated previously, the stringency conditions can be selected to promote hybridization.

35

In one format, PCR provides for the hybridization of non-complementary probes to different strands of a double-stranded nucleic acid template molecule (ie. a DNA/RNA, RNA/RNA or DNA/DNA template), such that the hybridized probes are positioned to facilitate the 5'-to 3' synthesis of nucleic acid in the intervening region, under the control of a thermostable DNA polymerase enzyme. In accordance with this embodiment, one sense probe and one antisense probe as described herein would be used to amplify DNA from the hybrid RNA/DNA template or cDNA.

In the present context, the cDNA would generally be produced by reverse transcription of mRNA present in the sample being tested (ie. RT-PCR). RT-PCR is particularly useful when it is desirable to determine expression of a cancer-associated gene. It is also known to those skilled in the art to use mRNA/DNA hybrid molecules as a template for such amplification reactions, and, as a consequence, first strand cDNA synthesis is all that is required to be performed prior to the amplification reaction.

Variations of the embodiments described herein are described in detail by McPherson *et al.*, PCR: A Practical Approach. (series eds, D. Rickwood and B.D. Hames), IRL Press Limited, Oxford. pp1-253, 1991.

The amplification reaction detection means described *supra* can be further coupled to a classical hybridization reaction detection means to further enhance sensitivity and specificity of the inventive method, such as by hybridizing the amplified DNA with a probe which is different from any of the probes used in the amplification reaction.

Similarly, the hybridization reaction detection means described *supra* can be further coupled to a second hybridization step employing a probe which is different from the probe used in the first hybridization reaction.

The comparison to be performed in accordance with the present invention may be a visual comparison of the signal generated by the probe, or alternatively, a comparison of data integrated from the signal, such as, for example, data that have been corrected or normalized to allow for variation between samples. Such comparisons can be readily performed by those skilled in the art.

Polypeptides

Cancer-associated polypeptides are encoded by cancer-associated genes. It will be understood that such polypeptides include those polypeptide and fragments thereof that are homologous to the polypeptides encoded by the nucleotide sequences referred to in Tables 1-3, which are obtained from any source, for example related viral/bacterial proteins, cellular homologues and synthetic peptides, as well as variants or derivatives thereof.

Thus, the present invention encompasses the use of variants, homologues or derivatives of the cancer-associated proteins described in the accompanying Tables. In one embodiment, homologues are naturally occurring sequences, such as orthologues, tissue-specific isoforms and allelic variants.

In the context of the present invention, a homologous sequence is taken to include an amino acid sequence which is at least 60, 70, 80 or 90% identical, preferably at least 95 or 98% identical at the amino acid level over at least 20, 40, 60 or 80 amino acids with a sequence encoded by a nucleotide sequence referred to in any one of Tables 1-3. In particular, homology should typically be considered with respect to those regions of the sequence known to be essential for specific biological functions rather than non-essential neighbouring sequences.

Although amino acid homology can also be considered in terms of similarity (i.e. amino acid residues having similar chemical properties/functions), in the context of the present invention it is preferred to express homology in terms of sequence identity.

Homology comparisons are carried out as described above for nucleotide sequences with the appropriate modifications for amino acid sequences. For example when using the GCG Wisconsin Bestfit package (see below) the default gap penalty for amino acid sequences is -12 for a gap and -4 for each extension.

It should also be noted that where computer algorithms are used to align amino acid sequences, although the final % homology are measured in terms of identity, the alignment process itself is typically not based on an all-or-nothing pair comparison. Instead, a scaled similarity score matrix is generally used that assigns scores to each pairwise comparison based on chemical similarity or evolutionary distance. An example

of such a matrix commonly used is the BLOSUM62 matrix - the default matrix for the BLAST suite of programs. GCG Wisconsin programs generally use either the public default values or a custom symbol comparison table if supplied (see user manual for further details). It is preferred to use the public default values for the GCG package, or in
5 the case of other software, the default matrix, such as BLOSUM62.

The terms "variant" or "derivative" in relation to the amino acid sequences of the present invention includes any substitution of, variation of, modification of, replacement of, deletion of or addition of one (or more) amino acids from or to the sequence providing the resultant
10 amino acid sequence preferably has biological activity, preferably having at least 25 to 50% of the activity as the polypeptides referred to in the sequence listings, more preferably at least substantially the same activity. Particular details of biological activity for each polypeptide are given in Tables 1-3.

15 Thus, the polypeptides referred to in Tables 1-3 and homologues thereof, are modified for use in the present invention. Typically, modifications are made that maintain the activity of the sequence. Thus, in one embodiment, amino acid substitutions are made, for example from 1, 2 or 3 to 10, 20 or 30 substitutions provided that the modified sequence retains at least about 25 to 50% of, or substantially the same activity.
20 However, in an alternative preferred embodiment, modifications to the amino acid sequences of a cancer-associated protein are made intentionally to reduce the biological activity of the polypeptide. For example truncated polypeptides that remain capable of binding to target molecules but lack functional effector domains are useful as inhibitors of the biological activity of the full length molecule.

25 In general, preferably less than 20%, 10% or 5% of the amino acid residues of a variant or derivative are altered as compared with the corresponding region of the polypeptides referred to in Tables 1-3.

30 Amino acid substitutions may include the use of non-naturally occurring analogues, for example to increase blood plasma half-life of a therapeutically administered polypeptide (see below for further details on the production of peptide derivatives for use in therapy).

Conservative substitutions are made, for example according to the Table below. Amino
35 acids in the same block in the second column and preferably in the same line in the third column are substituted for each other:

ALIPHATIC	Non-polar	G A P
		I L V
	Polar - uncharged	C S T M
		N Q
	Polar - charged	D E
		K R
AROMATIC		H F W Y

Cancer-associated proteins also include fragments of the above mentioned full length polypeptides and variants thereof, including fragments of the sequences referred to in
 5 Tables 1-3 and homologues thereof. Preferred fragments include those which include an epitope. Suitable fragments will be at least about 6 or 8, e.g. at least 10, 12, 15 or 20 amino acids in length. They may also be less than 200, 100 or 50 amino acids in length. Polypeptide fragments may contain one or more (e.g. 2, 3, 5, or 10) substitutions, deletions or insertions, including conserved substitutions. Where substitutions, deletion and/or
 10 insertions have been made, for example by means of recombinant technology, preferably less than 20%, 10% or 5% of the amino acid residues depicted in the sequence listings are altered.

Cancer-associated proteins are preferably in a substantially isolated form. It will be
 15 understood that the protein are mixed with carriers or diluents which will not interfere with the intended purpose of the protein and still be regarded as substantially isolated. A cancer-associated protein of the invention may also be in a substantially purified form, in which case it will generally comprise the protein in a preparation in which more than 90%, e.g. 95%, 98% or 99% pure as determined by SDS/PAGE or other art-recognized
 20 means for assessing protein purity.

Protein Production

For producing full-length polypeptides or immunologically active derivatives thereof by recombinant means, a protein-encoding region comprising at least about 15 contiguous
 25 nucleotides of the protein-encoding region of a nucleic acid referred to in any one of Tables 1-3 is placed in operable connection with a promoter or other regulatory sequence capable of regulating expression in a cell-free system or cellular system.

Reference herein to a "promoter" is to be taken in its broadest context and includes the transcriptional regulatory sequences of a classical genomic gene, including the TATA box which is required for accurate transcription initiation, with or without a CCAAT box sequence and additional regulatory elements (i.e., upstream activating sequences, enhancers and silencers) which alter gene expression in response to developmental and/or external stimuli, or in a tissue-specific manner. In the present context, the term "promoter" is also used to describe a recombinant, synthetic or fusion molecule, or derivative which confers, activates or enhances the expression of a nucleic acid molecule to which it is operably connected, and which encodes the polypeptide or peptide fragment. Preferred promoters can contain additional copies of one or more specific regulatory elements to further enhance expression and/or to alter the spatial expression and/or temporal expression of the said nucleic acid molecule.

Placing a nucleic acid molecule under the regulatory control of, i.e., "in operable connection with", a promoter sequence means positioning said molecule such that expression is controlled by the promoter sequence. Promoters are generally positioned 5' (upstream) to the coding sequence that they control. To construct heterologous promoter/structural gene combinations, it is generally preferred to position the promoter at a distance from the gene transcription start site that is approximately the same as the distance between that promoter and the gene it controls in its natural setting, i.e., the gene from which the promoter is derived. Furthermore, the regulatory elements comprising a promoter are usually positioned within 2 kb of the start site of transcription of the gene. As is known in the art, some variation in this distance can be accommodated without loss of promoter function. Similarly, the preferred positioning of a regulatory sequence element with respect to a heterologous gene to be placed under its control is defined by the positioning of the element in its natural setting, i.e., the genes from which it is derived. Again, as is known in the art, some variation in this distance can also occur.

The prerequisite for producing intact polypeptides and peptides in bacteria such as *E. coli* is the use of a strong promoter with an effective ribosome binding site. Typical promoters suitable for expression in bacterial cells such as *E. coli* include, but are not limited to, the *lacZ* promoter, temperature-sensitive λ_L or λ_R promoters, T7 promoter or the IPTG-inducible *tac* promoter. A number of other vector systems for expressing the nucleic acid molecule of the invention in *E. coli* are well-known in the art and are described, for example, in Ausubel *et al* (*In: Current Protocols in Molecular Biology*. Wiley Interscience, ISBN 047150338, 1987) or Sambrook *et al* (*In: Molecular cloning*. A

laboratory manual, second edition, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1989). Numerous plasmids with suitable promoter sequences for expression in bacteria and efficient ribosome binding sites have been described, such as for example, pKC30 (λ : Shimatake and Rosenberg, *Nature* 292, 128, 1981); pKK173-3 (*tac*: Amann and Brosius, *Gene* 40, 183, 1985), pET-3 (T7: Studier and Moffat, *J. Mol. Biol.* 189, 113, 1986); the pBAD/TOPO or pBAD/Thio-TOPO series of vectors containing an arabinose-inducible promoter (Invitrogen, Carlsbad, CA), the latter of which is designed to also produce fusion proteins with thioredoxin to enhance solubility of the expressed protein; the pFLEX series of expression vectors (Pfizer Inc., CT, USA); or the pQE series of expression vectors (Qiagen, CA), amongst others.

Typical promoters suitable for expression in viruses of eukaryotic cells and eukaryotic cells include the SV40 late promoter, SV40 early promoter and cytomegalovirus (CMV) promoter, CMV IE (cytomegalovirus immediate early) promoter amongst others. Preferred vectors for expression in mammalian cells (eg. 293, COS, CHO, 293T cells) include, but are not limited to, the pcDNA vector suite supplied by Invitrogen, in particular pcDNA 3.1 myc-His-tag comprising the CMV promoter and encoding a C-terminal 6xHis and MYC tag; and the retrovirus vector pSRatkneo (Muller *et al.*, *Mol. Cell. Biol.*, 11, 1785, 1991). The vector pcDNA 3.1 myc-His (Invitrogen) is particularly preferred for expressing a secreted form of a protein in 293T cells, wherein the expressed peptide or protein can be purified free of conspecific proteins, using standard affinity techniques that employ a Nickel column to bind the protein via the His tag.

A wide range of additional host/vector systems suitable for expressing polypeptides or immunological derivatives thereof are available publicly, and described, for example, in Sambrook *et al* (*In*: Molecular cloning. A laboratory manual, second edition, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y., 1989).

Means for introducing the isolated nucleic acid molecule or a gene construct comprising same into a cell for expression are well-known to those skilled in the art. The technique used for a given organism depends on the known successful techniques. Means for introducing recombinant DNA into animal cells include microinjection, transfection mediated by DEAE-dextran, transfection mediated by liposomes such as by using lipofectamine (Gibco, MD, USA) and/or cellfectin (Gibco, MD, USA), PEG-mediated DNA uptake, electroporation and microparticle bombardment such as by using DNA-coated tungsten or gold particles (Agracetus Inc., WI, USA) amongst others.

For producing mutants, nucleotide insertion derivatives of the protein-encoding region are produced by making 5' and 3' terminal fusions, or by making intra-sequence insertions of single or multiple nucleotides or nucleotide analogues. Insertion nucleotide
5 sequence variants are produced by introducing one or more nucleotides or nucleotide analogues into a predetermined site in the nucleotide sequence of said sequence, although random insertion is also possible with suitable screening of the resulting product being performed. Deletion variants are produced by removing one or more nucleotides from the nucleotide sequence. Substitutional nucleotide variants are produced by
10 substituting at least one nucleotide in the sequence with a different nucleotide or a nucleotide analogue in its place, with the immunologically active derivative encoded therefor having an identical amino acid sequence, or only a limited number of amino acid modifications that do not alter its antigenicity compared to the base peptide or its ability to bind antibodies prepared against the base peptide. Such mutant derivatives will
15 preferably have at least 80% identity with the base amino acid sequence from which they are derived.

Preferred immunologically active derivatives of a full-length polypeptide encoded by a gene referred to in any one of Tables 1-3 will comprise at least about 5-10 contiguous
20 amino acids of the full-length amino acid sequence, more preferably at least about 10-20 contiguous amino acids in length, and even more preferably 20-30 contiguous amino acids in length.

For the purposes of producing derivatives using standard peptide synthesis techniques,
25 such as, for example, Fmoc chemistry, a length not exceeding about 30-50 amino acids in length is preferred, as longer peptides are difficult to produce at high efficiency. Longer peptide fragments are readily achieved using recombinant DNA techniques wherein the peptide is expressed in a cell-free or cellular expression system comprising nucleic acid encoding the desired peptide fragment.

30

It will be apparent to the skilled artisan that any sufficiently antigenic region of at least about 5-10 amino acid residues can be used to prepare antibodies that bind generally to the polypeptides listed in Tables 1-3.

35 An expressed protein or synthetic peptide is preferably produced as a recombinant fusion protein, such as for example, to aid in extraction and purification. To produce a fusion

polypeptide, the open reading frames are covalently linked in the same reading frame, such as, for example, using standard cloning procedures as described by Ausubel *et al.* (Current Protocols in Molecular Biology, Wiley Interscience, ISBN 047150338, 1992), and expressed under control of a promoter. Examples of fusion protein partners include glutathione-S-transferase (GST), FLAG, hexahistidine, GAL4 (DNA binding and/or transcriptional activation domains) and β -galactosidase. It may also be convenient to include a proteolytic cleavage site between the fusion protein partner and the protein sequence of interest to allow removal of fusion protein sequences. Preferably the fusion protein will not hinder the immune function of the target protein.

In a particularly preferred embodiment, polypeptides are produced substantially free of conspecific proteins. Such purity can be assessed by standard procedures, such as, for example, SDS/polyacrylamide gel electrophoresis, 2-dimensional gel electrophoresis, chromatography, amino acid composition analysis, or amino acid sequence analysis.

To produce isolated polypeptides or fragments, eg., for antibody production, standard protein purification techniques may be employed. For example, gel filtration, ion exchange chromatography, reverse phase chromatography, or affinity chromatography, or a combination of any one or more said procedures, may be used. High pressure and low pressure procedures can also be employed, such as, for example, FPLC, or HPLC. To isolate the full-length proteins or peptide fragments comprising more than about 50-100 amino acids in length, it is particularly preferred to express the polypeptide in a suitable cellular expression system in combination with a suitable affinity tag, such as a 6xHis tag, and to purify the polypeptide using an affinity step that bonds it via the tag (*supra*). Optionally, the tag may then be cleaved from the expressed polypeptide.

Alternatively, for short immunologically active derivatives of a full-length polypeptide, preferably those peptide fragments comprising less than about 50 amino acids in length, chemical synthesis techniques are conveniently used. As will be known to those skilled in the art, such techniques may also produce contaminating peptides that are shorter than the desired peptide, in which case the desired peptide is conveniently purified using reverse phase and/or ion exchange chromatography procedures at high pressure (ie. HPLC or FPLC).

Antibodies

The invention also provides monoclonal or polyclonal antibodies that bind specifically to polypeptides of the invention or fragments thereof. Thus, the present invention further provides a process for the production of monoclonal or polyclonal antibodies to polypeptides of the invention.

5

The phrase "binds specifically" to a polypeptide means that the binding of the antibody to the protein or peptide is determinative of the presence of the protein, in a heterogeneous population of proteins and other biologics. Thus, under designated immunoassay conditions, the specified antibodies bind to a particular protein at least two times the background and more typically more than 10 to 100 times background. Typically, antibodies of the invention bind to a protein of interest with a K_d of at least about 0.1 mM, more usually at least about 1 μ M, preferably at least about 0.1 μ M, and most preferably at least, 0.01 μ M.

10

Reference herein to antibody or antibodies includes whole polyclonal and monoclonal antibodies, and parts thereof, either alone or conjugated with other moieties. Antibody parts include Fab and $F(ab)_2$ fragments and single chain antibodies. The antibodies may be made *in vivo* in suitable laboratory animals, or, in the case of engineered antibodies (Single Chain Antibodies or SCABS, etc) using recombinant DNA techniques *in vitro*.

20

In accordance with this aspect of the invention, the antibodies may be produced for the purposes of immunizing the subject, in which case high titer or neutralizing antibodies that bind to a B cell epitope will be especially preferred. Suitable subjects for immunization will, of course, depend upon the immunizing antigen or antigenic B cell epitope. It is contemplated that the present invention will be broadly applicable to the immunization of a wide range of animals, such as, for example, farm animals (e.g. horses, cattle, sheep, pigs, goats, chickens, ducks, turkeys, and the like), laboratory animals (e.g. rats, mice, guinea pigs, rabbits), domestic animals (cats, dogs, birds and the like), feral or wild exotic animals (e.g. possums, cats, pigs, buffalo, wild dogs and the like) and humans.

25

30

Alternatively, the antibodies may be for commercial or diagnostic purposes, in which case the subject to whom the diagnostic/prognostic protein or immunogenic fragment or epitope thereof is administered will most likely be a laboratory or farm animal. A wide range of animal species are used for the production of antisera. Typically the animal used for production of antisera is a rabbit, a mouse, rat, hamster, guinea pig, goat,

35

sheep, pig, dog, horse, or chicken. Because of the relatively large blood volume of rabbits, a rabbit is a preferred choice for production of polyclonal antibodies. However, as will be known to those skilled in the art, larger amounts of immunogen are required to obtain high antibodies from large animals as opposed to smaller animals such as mice.

5 In such cases, it will be desirable to isolate the antibody from the immunized animal.

Preferably, the antibody is a high titer antibody. By "high titer" means a sufficiently high titer to be suitable for use in diagnostic or therapeutic applications. As will be known in the art, there is some variation in what might be considered "high titer". For most
10 applications a titer of at least about 10^3 - 10^4 is preferred. More preferably, the antibody titer will be in the range from about 10^4 to about 10^5 , even more preferably in the range from about 10^5 to about 10^6 .

More preferably, in the case of B cell epitopes from pathogens, viruses or bacteria, the
15 antibody is a neutralizing antibody (i.e. it is capable of neutralizing the infectivity of the organism from which the B cell epitope is derived).

To generate antibodies, the diagnostic/prognostic protein or immunogenic fragment or epitope thereof, optionally formulated with any suitable or desired carrier, adjuvant, BRM,
20 or pharmaceutically acceptable excipient, is conveniently administered in the form of an injectable composition. Injection may be intranasal, intramuscular, sub-cutaneous, intravenous, intradermal, intraperitoneal, or by other known route. For intravenous injection, it is desirable to include one or more fluid and nutrient replenishers. Means for preparing and characterizing antibodies are well known in the art. (See, e.g.,
25 ANTIBODIES: A LABORATORY MANUAL, Cold Spring Harbor Laboratory, 1988, incorporated herein by reference).

The efficacy of the diagnostic/prognostic protein or immunogenic fragment or epitope thereof in producing an antibody is established by injecting an animal, for example, a
30 mouse, rat, rabbit, guinea pig, dog, horse, cow, goat or pig, with a formulation comprising the diagnostic/prognostic protein or immunogenic fragment or epitope thereof, and then monitoring the immune response to the B cell epitope, as described in the Examples. Both primary and secondary immune responses are monitored. The antibody titer is determined using any conventional immunoassay, such as, for example, ELISA, or radio
35 immunoassay.

The production of polyclonal antibodies may be monitored by sampling blood of the immunized animal at various points following immunization. A second, booster injection, may be given, if required to achieve a desired antibody titer. The process of boosting and titering is repeated until a suitable titer is achieved. When a desired level of immunogenicity is obtained, the immunized animal is bled and the serum isolated and stored, and/or the animal is used to generate monoclonal antibodies (Mabs).

For the production of monoclonal antibodies (Mabs) any one of a number of well-known techniques may be used, such as, for example, the procedure exemplified in US Patent No. 4,196,265, incorporated herein by reference.

For example, a suitable animal will be immunized with an effective amount of the diagnostic/prognostic protein or immunogenic fragment or epitope thereof under conditions sufficient to stimulate antibody producing cells. Rodents such as mice and rats are preferred animals, however, the use of rabbit, sheep, or frog cells is also possible. The use of rats may provide certain advantages, but mice are preferred, with the BALB/c mouse being most preferred as the most routinely used animal and one that generally gives a higher percentage of stable fusions.

Following immunization, somatic cells with the potential for producing antibodies, specifically B lymphocytes (B cells), are selected for use in the MAb generating protocol. These cells may be obtained from biopsied spleens, tonsils or lymph nodes, or from a peripheral blood sample. Spleen cells and peripheral blood cells are preferred, the former because they are a rich source of antibody-producing cells that are in the dividing plasmablast stage, and the latter because peripheral blood is easily accessible. Often, a panel of animals will have been immunized and the spleen of animal with the highest antibody titer removed. Spleen lymphocytes are obtained by homogenizing the spleen with a syringe. Typically, a spleen from an immunized mouse contains approximately 5×10^7 to 2×10^8 lymphocytes.

The B cells from the immunized animal are then fused with cells of an immortal myeloma cell, generally derived from the same species as the animal that was immunized with the diagnostic/prognostic protein or immunogenic fragment or epitope thereof. Myeloma cell lines suited for use in hybridoma-producing fusion procedures preferably are non-antibody-producing, have high fusion efficiency and enzyme deficiencies that render them incapable of growing in certain selective media which support the growth of only the

desired fused cells, or hybridomas. Any one of a number of myeloma cells may be used and these are known to those of skill in the art (e.g. murine P3-X63/Ag8, X63-Ag8.653, NS1/1.Ag 4 1, Sp210-Ag14, FO, NSO/U, MPC-11, MPC11-X45-GTG 1.7 and S194/5XX0; or rat R210.RCY3, Y3-Ag 1.2.3, IR983F and 4B210; and U-266, GM1500-GRG2, LICR-LON-HMy2 and UC729-6). A preferred murine myeloma cell is the NS-1 myeloma cell line (also termed P3-NS-1-Ag4-1), which is readily available from the NIGMS Human Genetic Mutant Cell Repository under Accession No. GM3573. Alternatively, a murine myeloma SP2/0 non-producer cell line that is 8-azaguanine-resistant is used.

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To generate hybrids of antibody-producing spleen or lymph node cells and myeloma cells, somatic cells are mixed with myeloma cells in a proportion between about 20:1 to about 1:1, respectively, in the presence of an agent or agents (chemical or electrical) that promote the fusion of cell membranes. Fusion methods using Sendai virus have been described by Kohler and Milstein, *Nature* 256, 495-497, 1975; and Kohler and Milstein, *Eur. J. Immunol.* 6, 511-519, 1976. Methods using polyethylene glycol (PEG), such as 37% (v/v) PEG, are described in detail by Gefter *et al.*, *Somatic Cell Genet.* 3, 231-236, 1977. The use of electrically induced fusion methods is also appropriate.

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Hybrids are amplified by culture in a selective medium comprising an agent that blocks the *de novo* synthesis of nucleotides in the tissue culture media. Exemplary and preferred agents are aminopterin, methotrexate and azaserine. Aminopterin and methotrexate block *de novo* synthesis of both purines and pyrimidines, whereas azaserine blocks only purine synthesis. Where aminopterin or methotrexate is used, the media is supplemented with hypoxanthine and thymidine as a source of nucleotides (HAT medium). Where azaserine is used, the media is supplemented with hypoxanthine.

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The preferred selection medium is HAT, because only those hybridomas capable of operating nucleotide salvage pathways are able to survive in HAT medium, whereas myeloma cells are defective in key enzymes of the salvage pathway, (e.g., hypoxanthine phosphoribosyl transferase or HPRT), and they cannot survive. B cells can operate this salvage pathway, but they have a limited life span in culture and generally die within about two weeks. Accordingly, the only cells that can survive in the selective media are those hybrids formed from myeloma and B cells.

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The amplified hybridomas are subjected to a functional selection for antibody specificity and/or titer, such as, for example, by immunoassay (e.g. radioimmunoassay, enzyme immunoassay, cytotoxicity assay, plaque assay, dot immunobinding assay, and the like).

- 5 The selected hybridomas are serially diluted and cloned into individual antibody-producing cell lines, which clones can then be propagated indefinitely to provide MAbs. The cell lines may be exploited for MAb production in two basic ways. A sample of the hybridoma is injected, usually in the peritoneal cavity, into a histocompatible animal of the type that was used to provide the somatic and myeloma cells for the original fusion.
- 10 The injected animal develops tumors secreting the specific monoclonal antibody produced by the fused cell hybrid. The body fluids of the animal, such as serum or ascites fluid, can then be tapped to provide MAbs in high concentration. The individual cell lines could also be cultured *in vitro*, where the MAbs are naturally secreted into the culture medium from which they are readily obtained in high concentrations. MAbs
- 15 produced by either means may be further purified, if desired, using filtration, centrifugation and various chromatographic methods such as HPLC or affinity chromatography.

- Monoclonal antibodies of the present invention also include anti-idiotypic antibodies
- 20 produced by methods well-known in the art. Monoclonal antibodies according to the present invention also may be monoclonal heteroconjugates, (i.e., hybrids of two or more antibody molecules). In another embodiment, monoclonal antibodies according to the invention are chimeric monoclonal antibodies. In one approach, the chimeric monoclonal antibody is engineered by cloning recombinant DNA containing the promoter, leader, and
- 25 variable-region sequences from a mouse anti-PSA producing cell and the constant-region exons from a human antibody gene. The antibody encoded by such a recombinant gene is a mouse-human chimera. Its antibody specificity is determined by the variable region derived from mouse sequences. Its isotype, which is determined by the constant region, is derived from human DNA.

- 30 In another embodiment, the monoclonal antibody according to the present invention is a "humanized" monoclonal antibody, produced by any one of a number of techniques well-known in the art. That is, mouse complementary determining regions ("CDRs") are transferred from heavy and light V-chains of the mouse Ig into a human V-domain,
- 35 followed by the replacement of some human residues in the framework regions of their

murine counterparts. "Humanized" monoclonal antibodies in accordance with this invention are especially suitable for use *in vivo* in diagnostic and therapeutic methods.

As stated above, the monoclonal antibodies and fragments thereof according to this invention are multiplied according to *in vitro* and *in vivo* methods well-known in the art. Multiplication *in vitro* is carried out in suitable culture media such as Dulbecco's modified Eagle medium or RPMI 1640 medium, optionally replenished by a mammalian serum such as fetal calf serum or trace elements and growth-sustaining supplements, e.g., feeder cells, such as normal mouse peritoneal exudate cells, spleen cells, bone marrow macrophages or the like. *In vitro* production provides relatively pure antibody preparations and allows scale-up to give large amounts of the desired antibodies. Techniques for large scale hybridoma cultivation under tissue culture conditions are known in the art and include homogenous suspension culture, (e.g., in an airlift reactor or in a continuous stirrer reactor or immobilized or entrapped cell culture).

Large amounts of the monoclonal antibody of the present invention also may be obtained by multiplying hybridoma cells *in vivo*. Cell clones are injected into mammals which are histocompatible with the parent cells, (e.g., syngeneic mice, to cause growth of antibody-producing tumors. Optionally, the animals are primed with a hydrocarbon, especially oils such as Pristane (tetramethylpentadecane) prior to injection.

In accordance with the present invention, fragments of the monoclonal antibody of the invention are obtained from monoclonal antibodies produced as described above, by methods which include digestion with enzymes such as pepsin or papain and/or cleavage of disulfide bonds by chemical reduction. Alternatively, monoclonal antibody fragments encompassed by the present invention are synthesized using an automated peptide synthesizer, or they may be produced manually using techniques well known in the art.

The monoclonal conjugates of the present invention are prepared by methods known in the art, e.g., by reacting a monoclonal antibody prepared as described above with, for instance, an enzyme in the presence of a coupling agent such as glutaraldehyde or periodate. Conjugates with fluorescein markers are prepared in the presence of these coupling agents, or by reaction with an isothiocyanate. Conjugates with metal chelates are similarly produced. Other moieties to which antibodies may be conjugated include

radionuclides such as, for example, ^3H , ^{125}I , ^{32}P , ^{35}S , ^{14}C , ^{51}Cr , ^{36}Cl , ^{57}Co , ^{58}Co , ^{59}Fe , ^{75}Se , and ^{152}Eu .

Radioactively labeled monoclonal antibodies of the present invention are produced according to well-known methods in the art. For instance, monoclonal antibodies are iodinated by contact with sodium or potassium iodide and a chemical oxidizing agent such as sodium hypochlorite, or an enzymatic oxidizing agent, such as lactoperoxidase. Monoclonal antibodies according to the invention may be labeled with technetium⁹⁹ by ligand exchange process, for example, by reducing pertechnetate with stannous solution, chelating the reduced technetium onto a Sephadex column and applying the antibody to this column or by direct labeling techniques, (e.g., by incubating pertechnetate, a reducing agent such as SnCl_2 , a buffer solution such as sodium-potassium phthalate solution, and the antibody).

Any immunoassay may be used to monitor antibody production by the diagnostic/prognostic protein or immunogenic fragment or epitope thereof. Immunoassays, in their most simple and direct sense, are binding assays. Certain preferred immunoassays are the various types of enzyme linked immunosorbent assays (ELISAs) and radioimmunoassays (RIA) known in the art. Immunohistochemical detection using tissue sections is also particularly useful. However, it will be readily appreciated that detection is not limited to such techniques, and Western blotting, dot blotting, FACS analyses, and the like may also be used.

Most preferably, the assay will be capable of generating quantitative results.

For example, antibodies are tested in simple competition assays. A known antibody preparation that binds to the B cell epitope and the test antibody are incubated with an antigen composition comprising the B cell epitope, preferably in the context of the native antigen. "Antigen composition" as used herein means any composition that contains some version of the B cell epitope in an accessible form. Antigen-coated wells of an ELISA plate are particularly preferred. In one embodiment, one would pre-mix the known antibodies with varying amounts of the test antibodies (e.g., 1:1, 1:10 and 1:100) for a period of time prior to applying to the antigen composition. If one of the known antibodies is labeled, direct detection of the label bound to the antigen is possible; comparison to an unmixed sample assay will determine competition by the test antibody and, hence, cross-

reactivity. Alternatively, using secondary antibodies specific for either the known or test antibody, one will be able to determine competition.

5 An antibody that binds to the antigen composition will be able to effectively compete for binding of the known antibody and thus will significantly reduce binding of the latter. The reactivity of the known antibodies in the absence of any test antibody is the control. A significant reduction in reactivity in the presence of a test antibody is indicative of a test antibody that binds to the B cell epitope (i.e., it cross-reacts with the known antibody).

10 In one exemplary ELISA, the antibodies against the diagnostic/prognostic protein or immunogenic fragment or B cell epitope are immobilized onto a selected surface exhibiting protein affinity, such as a well in a polystyrene microtiter plate. Then, a composition containing a peptide comprising the B cell epitope is added to the wells. After binding and washing to remove non-specifically bound immune complexes, the
15 bound epitope may be detected. Detection is generally achieved by the addition of a second antibody that is known to bind to the B cell epitope and is linked to a detectable label. This type of ELISA is a simple "sandwich ELISA". Detection may also be achieved by the addition of said second antibody, followed by the addition of a third antibody that has binding affinity for the second antibody, with the third antibody being linked to a
20 detectable label.

Antibodies of the invention may be bound to a solid support and/or packaged into kits in a suitable container along with suitable reagents, controls, instructions and the like.

25 *Immunoassay formats*

In one embodiment, a cancer-associated protein or an immunogenic fragment or epitope thereof is detected in a patient sample, wherein the level of the protein or immunogenic fragment or epitope in the sample is indicative of ovarian cancer or disease recurrence or an indicator of poor survival. Preferably, the method comprises contacting a biological
30 sample derived from the subject with an antibody capable of binding to a cancer-associated protein or an immunogenic fragment or epitope thereof, and detecting the formation of an antigen-antibody complex.

In another embodiment, an antibody against a cancer-associated protein or epitope
35 thereof is detected in a patient sample, wherein the level of the antibody in the sample is indicative of ovarian cancer or disease recurrence or an indicator of poor survival.

Preferably, the method comprises contacting a biological sample derived from the subject with a cancer-associated protein or an antigenic fragment eg., a B cell epitope or other immunogenic fragment thereof, and detecting the formation of an antigen-antibody complex.

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The diagnostic assays of the invention are useful for determining the progression of ovarian cancer or a metastasis thereof in a subject. In accordance with these prognostic applications of the invention, the level of a cancer-associated protein or an immunogenic fragment or epitope thereof in a biological sample is correlated with the disease state eg., as determined by clinical symptoms or biochemical tests (eg., CA125 levels).

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Accordingly, a further embodiment of the invention provides a method for detecting a cancer cell in a subject, said method comprising:

(i) determining the level of a cancer-associate protein in a test sample from said subject; and

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(ii) comparing the level determined at (i) to the level of said cancer-associated protein in a comparable sample from a healthy or normal individual,

wherein a level of said cancer-associate protein at (i) that is modified in the test sample relative to the comparable sample from the normal or healthy individual is indicative of the presence of a cancer cell in said subject.

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In one embodiment of the diagnostic/prognostic methods described herein, the biological sample is obtained previously from the subject. In accordance with such an embodiment, the prognostic or diagnostic method is performed *ex vivo*.

25

In yet another embodiment, the subject diagnostic/prognostic methods further comprise processing the sample from the subject to produce a derivative or extract that comprises the analyte.

Preferred detection systems contemplated herein include any known assay for detecting proteins or antibodies in a biological sample isolated from a human subject, such as, for example, SDS/PAGE, isoelectric focussing, 2-dimensional gel electrophoresis comprising SDS/PAGE and isoelectric focussing, an immunoassay, a detection based system using an antibody or non-antibody ligand of the protein, such as, for example, a small molecule (e.g. a chemical compound, agonist, antagonist, allosteric modulator, competitive inhibitor, or non-competitive inhibitor, of the protein). In accordance with

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these embodiments, the antibody or small molecule may be used in any standard solid phase or solution phase assay format amenable to the detection of proteins. Optical or fluorescent detection, such as, for example, using mass spectrometry, MALDI-TOF, biosensor technology, evanescent fiber optics, or fluorescence resonance energy transfer, is clearly encompassed by the present invention. Assay systems suitable for use in high throughput screening of mass samples, particularly a high throughput spectroscopy resonance method (e.g. MALDI-TOF, electrospray MS or nano-electrospray MS), are particularly contemplated.

Immunoassay formats are particularly preferred, eg., selected from the group consisting of, an immunoblot, a Western blot, a dot blot, an enzyme linked immunosorbent assay (ELISA), radioimmunoassay (RIA), enzyme immunoassay. Modified immunoassays utilizing fluorescence resonance energy transfer (FRET), isotope-coded affinity tags (ICAT), matrix-assisted laser desorption/ionization time of flight (MALDI-TOF), electrospray ionization (ESI), biosensor technology, evanescent fiber-optics technology or protein chip technology are also useful.

Preferably, the assay is a semi-quantitative assay or quantitative assay.

Standard solid phase ELISA formats are particularly useful in determining the concentration of a protein or antibody from a variety of patient samples.

In one form such as an assay involves immobilising a biological sample comprising antibodies against the cancer-associated protein or epitope, or alternatively an ovarian cancer-associated protein or an immunogenic fragment thereof, onto a solid matrix, such as, for example a polystyrene or polycarbonate microwell or dipstick, a membrane, or a glass support (e.g. a glass slide).

In the case of an antigen-based assay, an antibody that specifically binds an ovarian cancer-associated protein is brought into direct contact with the immobilised biological sample, and forms a direct bond with any of its target protein present in said sample. For an antibody-based assay, an immobilized ovarian cancer-associated protein or an immunogenic fragment or epitope thereof is contacted with the sample. The added antibody or protein in solution is generally labelled with a detectable reporter molecule, such as for example, a fluorescent label (e.g. FITC or Texas Red) or an enzyme (e.g. horseradish peroxidase (HRP)), alkaline phosphatase (AP) or β -galactosidase.

Alternatively, or in addition, a second labelled antibody can be used that binds to the first antibody or to the isolated/recombinant antigen. Following washing to remove any unbound antibody or antigen, as appropriate, the label is detected either directly, in the case of a fluorescent label, or through the addition of a substrate, such as for example
5 hydrogen peroxide, TMB, or toluidine, or 5-bromo-4-chloro-3-indol-beta-D-galactopyranoside (x-gal).

Such ELISA based systems are particularly suitable for quantification of the amount of a protein or antibody in a sample, such as, for example, by calibrating the detection system
10 against known amounts of a standard.

In another form, an ELISA consists of immobilizing an antibody that specifically binds an ovarian cancer-associated protein on a solid matrix, such as, for example, a membrane, a polystyrene or polycarbonate microwell, a polystyrene or polycarbonate dipstick or a
15 glass support. A patient sample is then brought into physical relation with said antibody, and the antigen in the sample is bound or 'captured'. The bound protein can then be detected using a labelled antibody. For example if the protein is captured from a human sample, an anti-human antibody is used to detect the captured protein. Alternatively, a third labelled antibody can be used that binds the second (detecting) antibody.

20 It will be apparent to the skilled person that the assay formats described herein are amenable to high throughput formats, such as, for example automation of screening processes, or a microarray format as described in Mendoza *et al*, Biotechniques 27(4): 778-788, 1999. Furthermore, variations of the above described assay will be apparent to
25 those skilled in the art, such as, for example, a competitive ELISA.

Alternatively, the presence of antibodies against the cancer-associated protein, or alternatively an ovarian cancer-associated protein or an immunogenic fragment thereof, is detected using a radioimmunoassay (RIA). The basic principle of the assay is the use of
30 a radiolabelled antibody or antigen to detect antibody antigen interactions. For example, an antibody that specifically binds to an ovarian cancer-associated protein can be bound to a solid support and a biological sample brought into direct contact with said antibody. To detect the bound antigen, an isolated and/or recombinant form of the antigen is radiolabelled is brought into contact with the same antibody. Following washing the
35 amount of bound radioactivity is detected. As any antigen in the biological sample inhibits binding of the radiolabelled antigen the amount of radioactivity detected is inversely

proportional to the amount of antigen in the sample. Such an assay may be quantitated by using a standard curve using increasing known concentrations of the isolated antigen.

As will be apparent to the skilled artisan, such an assay may be modified to use any
5 reporter molecule, such as, for example, an enzyme or a fluorescent molecule, in place of a radioactive label.

Western blotting is also useful for detecting an ovarian cancer-associated protein or an immunogenic fragment thereof. In such an assay protein from a biological sample is
10 separated using sodium dodecyl sulphate (SDS) polyacrylamide gel electrophoresis (SDS-PAGE) using techniques well known in the art and described in, for example, Scopes (*In: Protein Purification: Principles and Practice*, Third Edition, Springer Verlag, 1994). Separated proteins are then transferred to a solid support, such as, for example,
15 a membrane or more specifically PVDF membrane, using methods well known in the art, for example, electrotransfer. This membrane may then be blocked and probed with a labelled antibody or ligand that specifically binds an ovarian cancer-associated protein. Alternatively, a labelled secondary, or even tertiary, antibody or ligand can be used to detect the binding of a specific primary antibody.

20 High-throughput methods for detecting the presence or absence of antibodies, or alternatively ovarian cancer-associated protein or an immunogenic fragment thereof are particularly preferred.

In one embodiment, MALDI-TOF is used for the rapid identification of a protein.
25 Accordingly, there is no need to detect the proteins of interest using an antibody or ligand that specifically binds to the protein of interest. Rather, proteins from a biological sample are separated using gel electrophoresis using methods well known in the art and those proteins at approximately the correct molecular weight and/or isoelectric point are analysed using MALDI-TOF to determine the presence or absence of a protein of
30 interest.

Alternatively, MALDI or ESI or a combination of approaches is used to determine the concentration of a particular protein in a biological sample, such as, for example sputum. Such proteins are preferably well characterised previously with regard to parameters
35 such as molecular weight and isoelectric point.

Biosensor devices generally employ an electrode surface in combination with current or impedance measuring elements to be integrated into a device in combination with the assay substrate (such as that described in U.S. Patent No. 5,567,301). An antibody or ligand that specifically binds to a protein of interest is preferably incorporated onto the surface of a biosensor device and a biological sample isolated from a patient (for example sputum that has been solubilised using the methods described herein) contacted to said device. A change in the detected current or impedance by the biosensor device indicates protein binding to said antibody or ligand. Some forms of biosensors known in the art also rely on surface plasmon resonance to detect protein interactions, whereby a change in the surface plasmon resonance surface of reflection is indicative of a protein binding to a ligand or antibody (U.S. Patent No. 5,485,277 and 5,492,840).

Biosensors are of particular use in high throughput analysis due to the ease of adapting such systems to micro- or nano-scales. Furthermore, such systems are conveniently adapted to incorporate several detection reagents, allowing for multiplexing of diagnostic reagents in a single biosensor unit. This permits the simultaneous detection of several epitopes in a small amount of body fluids.

Evanescent biosensors are also preferred as they do not require the pretreatment of a biological sample prior to detection of a protein of interest. An evanescent biosensor generally relies upon light of a predetermined wavelength interacting with a fluorescent molecule, such as for example, a fluorescent antibody attached near the probe's surface, to emit fluorescence at a different wavelength upon binding of the diagnostic protein to the antibody or ligand.

To produce protein chips, the proteins, peptides, polypeptides, antibodies or ligands that are able to bind specific antibodies or proteins of interest are bound to a solid support such as for example glass, polycarbonate, polytetrafluoroethylene, polystyrene, silicon oxide, metal or silicon nitride. This immobilization is either direct (e.g. by covalent linkage, such as, for example, Schiff's base formation, disulfide linkage, or amide or urea bond formation) or indirect. Methods of generating a protein chip are known in the art and are described in for example U.S. Patent Application No. 20020136821, 20020192654, 20020102617 and U.S. Patent No. 6,391,625. In order to bind a protein to a solid support it is often necessary to treat the solid support so as to create chemically reactive groups on the surface, such as, for example, with an aldehyde-containing silane reagent.

Alternatively, an antibody or ligand may be captured on a microfabricated polyacrylamide gel pad and accelerated into the gel using microelectrophoresis as described in, Arenkov *et al. Anal. Biochem.* 278:123-131, 2000.

- 5 A protein chip is preferably generated such that several proteins, ligands or antibodies are arrayed on said chip. This format permits the simultaneous screening for the presence of several proteins in a sample.

10 Alternatively, a protein chip may comprise only one protein, ligand or antibody, and be used to screen one or more patient samples for the presence of one polypeptide of interest. Such a chip may also be used to simultaneously screen an array of patient samples for a polypeptide of interest.

15 Preferably, a sample to be analysed using a protein chip is attached to a reporter molecule, such as, for example, a fluorescent molecule, a radioactive molecule, an enzyme, or an antibody that is detectable using methods well known in the art. Accordingly, by contacting a protein chip with a labelled sample and subsequent washing to remove any unbound proteins the presence of a bound protein is detected using methods well known in the art, such as, for example using a DNA microarray reader.

20 Alternatively, biomolecular interaction analysis-mass spectrometry (BIA-MS) is used to rapidly detect and characterise a protein present in complex biological samples at the low- to sub-fmole level (Nelson *et al. Electrophoresis* 21: 1155-1163, 2000). One technique useful in the analysis of a protein chip is surface enhanced laser
25 desorption/ionization-time of flight-mass spectrometry (SELDI-TOF-MS) technology to characterise a protein bound to the protein chip. Alternatively, the protein chip is analysed using ESI as described in U.S. Patent Application 20020139751.

30 As will be apparent to the skilled artisan, protein chips are particularly amenable to multiplexing of detection reagents. Accordingly, several antibodies or ligands each able to specifically bind a different peptide or protein may be bound to different regions of said protein chip. Analysis of a biological sample using said chip then permits the detecting of multiple proteins of interest, or multiple B cell epitopes of the ovarian cancer-associated protein. Multiplexing of diagnostic and prognostic markers is particularly contemplated in
35 the present invention.

In a further embodiment, the samples are analysed using ICAT, essentially as described in US Patent Application No. 20020076739. This system relies upon the labelling of a protein sample from one source (i.e. a healthy individual) with a reagent and the labelling of a protein sample from another source (i.e. a tuberculosis patient) with a second reagent that is chemically identical to the first reagent, but differs in mass due to isotope composition. It is preferable that the first and second reagents also comprise a biotin molecule. Equal concentrations of the two samples are then mixed, and peptides recovered by avidin affinity chromatography. Samples are then analysed using mass spectrometry. Any difference in peak heights between the heavy and light peptide ions directly correlates with a difference in protein abundance in a biological sample. The identity of such proteins may then be determined using a method well known in the art, such as, for example MALDI-TOF, or ESI.

As will be apparent to those skilled in the art a diagnostic or prognostic assay described herein may be a multiplexed assay. As used herein the term "multiplex", shall be understood not only to mean the detection of two or more diagnostic or prognostic markers in a single sample simultaneously, but also to encompass consecutive detection of two or more diagnostic or prognostic markers in a single sample, simultaneous detection of two or more diagnostic or prognostic markers in distinct but matched samples, and consecutive detection of two or more diagnostic or prognostic markers in distinct but matched samples. As used herein the term "matched samples" shall be understood to mean two or more samples derived from the same initial biological sample, or two or more biological samples isolated at the same point in time.

Accordingly, a multiplexed assay may comprise an assay that detects several antibodies and/or epitopes in the same reaction and simultaneously, or alternatively, it may detect other one or more antigens/antibodies in addition to one or more antibodies and/or epitopes. As will be apparent to the skilled artisan, if such an assay is antibody or ligand based, both of these antibodies must function under the same conditions.

Diagnostic assay kits

A further aspect of the present invention provides a kit for detecting *M. tuberculosis* infection in a biological sample. In one embodiment, the kit comprises:

- (i) one or more isolated antibodies that bind to an ovarian cancer-associated protein or an immunogenic fragment or epitope thereof; and
- (ii) means for detecting the formation of an antigen-antibody complex.

In an alternative embodiment, the kit comprises:

- (i) an isolated or recombinant ovarian cancer-associated protein or an immunogenic fragment or epitope thereof; and
- 5 (ii) means for detecting the formation of an antigen-antibody complex.

Optionally, the kit further comprises means for the detection of the binding of an antibody, fragment thereof or a ligand to an ovarian cancer-associated protein. Such means include a reporter molecule such as, for example, an enzyme (such as
10 horseradish peroxidase or alkaline phosphatase), a substrate, a cofactor, an inhibitor, a dye, a radionucleotide, a luminescent group, a fluorescent group, biotin or a colloidal particle, such as colloidal gold or selenium. Preferably such a reporter molecule is directly linked to the antibody or ligand.

15 In yet another embodiment, a kit may additionally comprise a reference sample. Such a reference sample.

In another embodiment, a reference sample comprises a peptide that is detected by an antibody or a ligand. Preferably, the peptide is of known concentration. Such a peptide
20 is of particular use as a standard. Accordingly various known concentrations of such a peptide may be detected using a prognostic or diagnostic assay described herein.

In yet another embodiment, a kit comprises means for protein isolation (Scopes (*In: Protein Purification: Principles and Practice*, Third Edition, Springer Verlag, 1994).

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Bioinformatics

The ability to identify genes that are over or under expressed in ovarian cancer can additionally provide high-resolution, high-sensitivity datasets which are used in the areas of diagnostics, therapeutics, drug development, pharmacogenetics, protein structure,
30 biosensor development, and other related areas. For example, the expression profiles are used in diagnostic or prognostic evaluation of patients with ovarian cancer. Or as another example, subcellular toxicological information are generated to better direct drug structure and activity correlation (see Anderson, *Pharmaceutical Proteomics: Targets, Mechanism, and Function*, paper presented at the IBC Proteomics conference,
35 Coronado, CA (June 11-12, 1998)). Subcellular toxicological information can also be utilized in a biological sensor device to predict the likely toxicological effect of chemical

exposures and likely tolerable exposure thresholds (see U.S. Patent No. 5,811,231). Similar advantages accrue from datasets relevant to other biomolecules and bioactive agents (e.g., nucleic acids, saccharides, lipids, drugs, and the like).

5 Thus, in another embodiment, the present invention provides a database that includes at least one set of assay data. The data contained in the database is acquired, e.g., using array analysis either singly or in a library format. The database are in substantially any form in which data are maintained and transmitted, but is preferably an electronic database. The electronic database of the invention are maintained on any electronic
10 device allowing for the storage of and access to the database, such as a personal computer, but is preferably distributed on a wide area network, such as the World Wide Web.

The focus of the present section on databases that include peptide sequence data is for
15 clarity of illustration only. It will be apparent to those of skill in the art that similar databases are assembled for any assay data acquired using an assay of the invention.

The compositions and methods for identifying and/or quantitating the relative and/or absolute abundance of a variety of molecular and macromolecular species from a
20 biological sample undergoing ovarian cancer, i.e., the identification of ovarian cancer-associated sequences described herein, provide an abundance of information, which are correlated with pathological conditions, predisposition to disease, drug testing, therapeutic monitoring, gene-disease causal linkages, identification of correlates of immunity and physiological status, among others. Although the data generated from the
25 assays of the invention is suited for manual review and analysis, in a preferred embodiment, prior data processing using high-speed computers is utilized.

An array of methods for indexing and retrieving biomolecular information is known in the art. For example, U.S. Patents 6,023,659 and 5,966,712 disclose a relational database
30 system for storing biomolecular sequence information in a manner that allows sequences to be catalogued and searched according to one or more protein function hierarchies. U.S. Patent 5,953,727 discloses a relational database having sequence records containing information in a format that allows a collection of partial-length DNA sequences to be catalogued and searched according to association with one or more
35 sequencing projects for obtaining full-length sequences from the collection of partial length sequences. U.S. Patent 5,706,498 discloses a gene database retrieval system for

- making a retrieval of a gene sequence similar to a sequence data item in a gene database based on the degree of similarity between a key sequence and a target sequence. U.S. Patent 5,538,897 discloses a method using mass spectroscopy fragmentation patterns of peptides to identify amino acid sequences in computer
- 5 databases by comparison of predicted mass spectra with experimentally-derived mass spectra using a closeness-of-fit measure. U.S. Patent 5,926,818 discloses a multi-dimensional database comprising a functionality for multi-dimensional data analysis described as on-line analytical processing (OLAP), which entails the consolidation of projected and actual data according to more than one consolidation path or dimension.
- 10 U.S. Patent 5,295,261 reports a hybrid database structure in which the fields of each database record are divided into two classes, navigational and informational data, with navigational fields stored in a hierarchical topological map which are viewed as a tree structure or as the merger of two or more such tree structures.
- 15 See also Mount *et al.*, *Bioinformatics* (2001); *Biological Sequence Analysis: Probabilistic Models of Proteins and Nucleic Acids* (Durbin *et al.*, eds., 1999); *Bioinformatics: A Practical Guide to the Analysis of Genes and Proteins* (Baxeavanis & Oeullette eds., 1998)); Rashidi & Buehler, *Bioinformatics: Basic Applications in Biological Science and Medicine* (1999); *Introduction to Computational Molecular Biology* (Setubal *et al.*, eds
- 20 1997); *Bioinformatics: Methods and Protocols* (Misener & Krawetz, eds, 2000); *Bioinformatics: Sequence, Structure, and Databanks: A Practical Approach* (Higgins & Taylor, eds., 2000); Brown, *Bioinformatics: A Biologist's Guide to Biocomputing and the Internet* (2001); Han & Kamber, *Data Mining: Concepts and Techniques* (2000); and Waterman, *Introduction to Computational Biology: Maps, Sequences, and Genomes*
- 25 (1995).

The present invention provides a computer database comprising a computer and software for storing in computer-retrievable form assay data records cross-tabulated, e.g., with data specifying the source of the target-containing sample from which each

30 sequence specificity record was obtained.

In an exemplary embodiment, at least one of the sources of target-containing sample is from a control tissue sample known to be free of pathological disorders. In a variation, at least one of the sources is a known pathological tissue specimen, e.g., a neoplastic

35 lesion or another tissue specimen to be analyzed for prostate cancer. In another variation, the assay records cross-tabulate one or more of the following parameters for

each target species in a sample: (1) a unique identification code, which can include, e.g., a target molecular structure and/or characteristic separation coordinate (e.g., electrophoretic coordinates); (2) sample source; and (3) absolute and/or relative quantity of the target species present in the sample.

5

The invention also provides for the storage and retrieval of a collection of target data in a computer data storage apparatus, which can include magnetic disks, optical disks, magneto-optical disks, DRAM, SRAM, SGRAM, SDRAM, RDRAM, DDR RAM, magnetic bubble memory devices, and other data storage devices, including CPU registers and
10 on-CPU data storage arrays. Typically, the target data records are stored as a bit pattern in an array of magnetic domains on a magnetizable medium or as an array of charge states or transistor gate states, such as an array of cells in a DRAM device (e.g., each cell comprised of a transistor and a charge storage area, which are on the transistor). In one embodiment, the invention provides such storage devices, and computer systems
15 built therewith, comprising a bit pattern encoding a protein expression fingerprint record comprising unique identifiers for at least 10 target data records cross-tabulated with target source.

When the target is a peptide or nucleic acid, the invention preferably provides a method
20 for identifying related peptide or nucleic acid sequences, comprising performing a computerised comparison between a peptide or nucleic acid sequence assay record stored in or retrieved from a computer storage device or database and at least one other sequence. The comparison can include a sequence analysis or comparison algorithm or computer program embodiment thereof (e.g., BLAST, FASTA, TFASTA, GAP, BESTFIT
25 – see above) and/or the comparison are of the relative amount of a peptide or nucleic acid sequence in a pool of sequences determined from a polypeptide or nucleic acid sample of a specimen.

The invention also preferably provides a magnetic disk, such as an IBM-compatible
30 (DOS, Windows, Windows95/98/2000, Windows NT, OS/2) or other format (e.g., Linux, SunOS, Solaris, AIX, SCO Unix, VMS, MV; Macintosh, etc.) floppy diskette or hard (fixed, Winchester) disk drive, comprising a bit pattern encoding data from an assay of the invention in a file format suitable for retrieval and processing in a computerized sequence analysis, comparison, or relative quantitation method.

35

The invention also provides a network, comprising a plurality of computing devices linked via a data link, such as an Ethernet cable (coax or IOBaseT), telephone line, ISDN line, wireless network, optical fiber, or other suitable signal transmission medium, whereby at least one network device (e.g., computer, disk array, etc.) comprises a pattern of magnetic domains (e.g., magnetic disk) and/or charge domains (e.g., an array of DRAM cells) composing a bit pattern encoding data acquired from an assay of the invention.

The invention also provides a method for transmitting assay data that includes generating an electronic signal on an electronic communications device, such as a modem, ISDN terminal adapter, DSL, cable modem, ATM switch, or the like, wherein the signal includes (in native or encrypted format) a bit pattern encoding data from an assay or a database comprising a plurality of assay results obtained by the method of the invention.

In a preferred embodiment, the invention provides a computer system for comparing a query target to a database containing an array of data structures, such as an assay result obtained by the method of the invention, and ranking database targets based on the degree of identity and gap weight to the target data. A central processor is preferably initialized to load and execute the computer program for alignment and/or comparison of the assay results. Data for a query target is entered into the central processor via an I/O device. Execution of the computer program results in the central processor retrieving the assay data from the data file, which comprises a binary description of an assay result.

The target data or record and the computer program are transferred to secondary memory, which is typically random access memory (e.g., DRAM, SRAM, SGRAM, or SDRAM). Targets are ranked according to the degree of correspondence between a selected assay characteristic (e.g., binding to a selected affinity moiety) and the same characteristic of the query target and results are output via an I/O device. For example, a central processor are a conventional computer (e.g., Intel Pentium, PowerPC, Alpha, PA-8000, SPARC, MIPS 4400, MIPS 10000, VAX, etc.); a program are a commercial or public domain molecular biology software package (e.g., UWGCG Sequence Analysis Software, Darwin); a data file are an optical or magnetic disk, a data server, a memory device (e.g., DRAM, SRAM, SGRAM, SDRAM, EPROM, bubble memory, flash memory, etc.); an I/O device are a terminal comprising a video display and a keyboard, a modem, an ISDN terminal adapter, an Ethernet port, a punched card reader, a magnetic strip reader, or other suitable I/O device.

The invention also preferably provides the use of a computer system, such as that described above, which comprises: (1) a computer; (2) a stored bit pattern encoding a collection of peptide sequence specificity records obtained by the methods of the invention, which are stored in the computer; (3) a comparison target, such as a query target; and (4) a program for alignment and comparison, typically with rank-ordering of comparison results on the basis of computed similarity values.

Transgenic Animals Expressing Ovarian Cancer-associated proteins and "Knock-Out"

Animals

The present invention also contemplates transgenic animals which are transgenic by virtue of comprising a polynucleotide of the invention, i.e. animals transformed with a cancer-associated gene of the invention. Suitable animals are generally from the phylum chordata. Chordates includes vertebrate groups such as mammals, birds, reptiles and amphibians. Particular examples of mammals include non-human primates, cats, dogs, ungulates such as cows, goats, pigs, sheep and horses and rodents such as mice, rats, gerbils and hamsters. Transgenic animals within the meaning of the present invention are non-human animals and the production of transgenic humans is specifically excluded.

Techniques for producing transgenic animals are well known in the art. A useful general textbook on this subject is Houdebine, *Transgenic animals – Generation and Use* (Harwood Academic, 1997) – an extensive review of the techniques used to generate transgenic animals from fish to mice and cows.

Advances in technologies for embryo micromanipulation now permit introduction of heterologous DNA into, for example, fertilized mammalian ova. For instance, totipotent or pluripotent stem cells are transformed by microinjection, calcium phosphate mediated precipitation, liposome fusion, retroviral infection or other means, the transformed cells are then introduced into the embryo, and the embryo then develops into a transgenic animal. In a highly preferred method, developing embryos are infected with a retrovirus containing the desired DNA, and transgenic animals produced from the infected embryo. In a most preferred method, however, the appropriate DNAs are coinjected into the pronucleus or cytoplasm of embryos, preferably at the single cell stage, and the embryos allowed to develop into mature transgenic animals. Those techniques as well known. See reviews of standard laboratory procedures for microinjection of heterologous DNAs into

mammalian fertilized ova, including Hogan *et al.*, Manipulating the Mouse Embryo, (Cold Spring Harbor Press 1986); Krimpenfort *et al.*, Bio/Technology 9:844 (1991); Palmiter *et al.*, Cell, 41: 343 (1985); Kraemer *et al.*, Genetic manipulation of the Mammalian Embryo, (Cold Spring Harbor Laboratory Press 1985); Hammer *et al.*, Nature, 315: 680 (1985);
5 Wagner *et al.*, U.S. Pat. No. 5,175,385; Krimpenfort *et al.*, U.S. Pat. No. 5,175,384, the respective contents of which are incorporated herein by reference

Another method used to produce a transgenic animal involves microinjecting a nucleic acid into pro-nuclear stage eggs by standard methods. Injected eggs are then cultured
10 before transfer into the oviducts of pseudopregnant recipients.

Transgenic animals may also be produced by nuclear transfer technology as described in Schnieke, A.E. *et al.*, 1997, Science, 278: 2130 and Cibelli, J.B. *et al.*, 1998, Science, 280: 1256. Using this method, fibroblasts from donor animals are stably transfected with
15 a plasmid incorporating the coding sequences for a binding domain or binding partner of interest under the control of regulatory. Stable transfectants are then fused to enucleated oocytes, cultured and transferred into female recipients.

Analysis of animals which may contain transgenic sequences would typically be
20 performed by either PCR or Southern blot analysis following standard methods.

By way of a specific example for the construction of transgenic mammals, such as cows, nucleotide constructs comprising a sequence encoding a binding domain fused to GFP are microinjected using, for example, the technique described in U.S. Pat. No. 4,873,191,
25 into oocytes which are obtained from ovaries freshly removed from the mammal. The oocytes are aspirated from the follicles and allowed to settle before fertilization with thawed frozen sperm capacitated with heparin and prefractionated by Percoll gradient to isolate the motile fraction.

30 The fertilized oocytes are centrifuged, for example, for eight minutes at 15,000 g to visualize the pronuclei for injection and then cultured from the zygote to morula or blastocyst stage in oviduct tissue-conditioned medium. This medium is prepared by using luminal tissues scraped from oviducts and diluted in culture medium. The zygotes must be placed in the culture medium within two hours following microinjection.

Oestrous is then synchronized in the intended recipient mammals, such as cattle, by administering coprostanol. Oestrous is produced within two days and the embryos are transferred to the recipients 5-7 days after estrous. Successful transfer are evaluated in the offspring by Southern blot.

5

Alternatively, the desired constructs are introduced into embryonic stem cells (ES cells) and the cells cultured to ensure modification by the transgene. The modified cells are then injected into the blastula embryonic stage and the blastulas replaced into pseudopregnant hosts. The resulting offspring are chimeric with respect to the ES and host cells, and nonchimeric strains which exclusively comprise the ES progeny are
10 obtained using conventional cross-breeding. This technique is described, for example, in WO91/10741.

In another embodiment, transgenic animals of the present invention are transgenic
15 "knock-out" animals where a specific gene corresponding to a polynucleotide referred to in Tables 1-3 has been rendered non-functional by homologous recombination. The generation of "knock-out" animals is similar to the production of other transgenic animals except that the polynucleotide constructs are designed to integrate into the endogenous genes and disrupt the function of the endogenous sequences. The generation of "knock-
20 out" animals is known in the art, including the design of suitable constructs that will recombine at the appropriate site in the genome.

In one embodiment, the heterologous sequence which it is desired to recombine into the genome of a target animal comprises a functional sequence but under the control of an
25 inducible promoter so that expression of the gene are regulated by administration of an endogenous molecule. This are advantageous where disruption of the gene is embryonic-lethal.

"Knock-out" animals are used as animal models for the study of gene function.
30

Therapeutic peptides

In accordance with this embodiment, ovarian cancer-associated proteins of the present invention are administered therapeutically to patients for a time and under conditions sufficient to ameliorate the growth of a tumor in the subject or to prevent tumor
35 recurrence.

It is preferred to use peptides that do not consist solely of naturally-occurring amino acids but which have been modified, for example to reduce immunogenicity, to increase circulatory half-life in the body of the patient, to enhance bioavailability and/or to enhance efficacy and/or specificity.

5

A number of approaches have been used to modify peptides for therapeutic application. One approach is to link the peptides or proteins to a variety of polymers, such as polyethylene glycol (PEG) and polypropylene glycol (PPG) – see for example U.S. Patent Nos. 5,091,176, 5,214,131 and US 5,264,209.

10

Replacement of naturally-occurring amino acids with a variety of uncoded or modified amino acids such as D-amino acids and N-methyl amino acids may also be used to modify peptides

15 Another approach is to use bifunctional crosslinkers, such as N-succinimidyl 3-(2 pyridyldithio) propionate, succinimidyl 6-[3-(2 pyridyldithio) propionamido] hexanoate, and sulfosuccinimidyl 6-[3-(2 pyridyldithio) propionamido]hexanoate (see US Patent 5,580,853).

20 It is desirable to use derivatives of the ovarian cancer-associated proteins of the invention which are conformationally constrained. Conformational constraint refers to the stability and preferred conformation of the three-dimensional shape assumed by a peptide. Conformational constraints include local constraints, involving restricting the conformational mobility of a single residue in a peptide; regional constraints, involving
25 restricting the conformational mobility of a group of residues, which residues may form some secondary structural unit; and global constraints, involving the entire peptide structure.

The active conformation of the peptide is stabilized by a covalent modification, such as
30 cyclization or by incorporation of gamma-lactam or other types of bridges. For example, side chains are cyclized to the backbone so as to create a L-gamma-lactam moiety on each side of the interaction site. See, generally, Hruby et al., "Applications of Synthetic Peptides," in Synthetic Peptides: A User's Guide: 259-345 (W. H. Freeman & Co. 1992). Cyclization is also achieved, for example, by formation of cystine bridges, coupling of
35 amino and carboxy terminal groups of respective terminal amino acids, or coupling of the amino group of a Lys residue or a related homolog with a carboxy group of Asp, Glu or a

related homolog. Coupling of the .alpha-amino group of a polypeptide with the epsilon-amino group of a lysine residue, using iodoacetic anhydride, are also undertaken. See Wood and Wetzel, 1992, Int'l J. Peptide Protein Res. 39: 533-39.

- 5 Another approach described in US 5,891,418 is to include a metal-ion complexing backbone in the peptide structure. Typically, the preferred metal-peptide backbone is based on the requisite number of particular coordinating groups required by the coordination sphere of a given complexing metal ion. In general, most of the metal ions that may prove useful have a coordination number of four to six. The nature of the
- 10 coordinating groups in the peptide chain includes nitrogen atoms with amine, amide, imidazole, or guanidino functionalities; sulfur atoms of thiols or disulfides; and oxygen atoms of hydroxy, phenolic, carbonyl, or carboxyl functionalities. In addition, the peptide chain or individual amino acids are chemically altered to include a coordinating group, such as for example oxime, hydrazino, sulfhydryl, phosphate, cyano, pyridino, piperidino,
- 15 or morpholino. The peptide construct are either linear or cyclic, however a linear construct is typically preferred. One example of a small linear peptide is Gly-Gly-Gly-Gly which has four nitrogens (an N₄ complexation system) in the back bone that can complex to a metal ion with a coordination number of four.
- 20 A further technique for improving the properties of therapeutic peptides is to use non-peptide peptidomimetics. A wide variety of useful techniques are used to elucidating the precise structure of a peptide. These techniques include amino acid sequencing, x-ray crystallography, mass spectroscopy, nuclear magnetic resonance spectroscopy, computer-assisted molecular modeling, peptide mapping, and combinations thereof.
- 25 Structural analysis of a peptide generally provides a large body of data which comprise the amino acid sequence of the peptide as well as the three-dimensional positioning of its atomic components. From this information, non-peptide peptidomimetics are designed that have the required chemical functionalities for therapeutic activity but are more stable, for example less susceptible to biological degradation. An example of this approach is
- 30 provided in US 5,811,512.

Techniques for chemically synthesising therapeutic peptides of the invention are described in the above references and also reviewed by Borgia and Fields, 2000, TibTech 18: 243-251 and described in detail in the references contained therein.

The ovarian cancer proteins, nucleic acids, and antibodies as described herein are used in drug screening assays to identify candidate compounds for use in treating ovarian cancer. The ovarian cancer-associated proteins, antibodies, nucleic acids, modified proteins and cells containing ovarian cancer sequences are used in drug screening
5 assays or by evaluating the effect of drug candidates on a "gene expression profile" or expression profile of polypeptides. In a preferred embodiment, the expression profiles are used, preferably in conjunction with high throughput screening techniques to allow monitoring for expression profile genes after treatment with a candidate agent (e.g., Zlokarnik, *et al.*, 1998, *Science* 279: 84-88); Heid, 1996, *Genome Res* 6: 986-94).

10

In a preferred embodiment, the ovarian cancer-associated proteins, antibodies, nucleic acids, modified proteins and cells containing the native or modified ovarian cancer-associated proteins are used in screening assays. That is, the present invention provides methods for screening for compounds/agents which modulate the ovarian cancer
15 phenotype or an identified physiological function of a ovarian cancer-associated protein. As above, this are done on an individual gene level or by evaluating the effect of drug candidates on a "gene expression profile". In a preferred embodiment, the expression profiles are used, preferably in conjunction with high throughput screening techniques to allow monitoring for expression profile genes after treatment with a candidate agent, see
20 Zlokarnik, *supra*.

Having identified the differentially expressed genes herein, a variety of assays are executed. In a preferred embodiment, assays are run on an individual gene or protein level. That is, having identified a particular gene as up regulated in ovarian cancer, test
25 compounds are screened for the ability to modulate gene expression or for binding to the ovarian cancer-associated protein. "Modulation" thus includes both an increase and a decrease in gene expression. The preferred amount of modulation will depend on the original change of the gene expression in normal versus tissue undergoing ovarian cancer, with changes of at least 10%, preferably 50%, more preferably 100-300%, and in
30 some embodiments 300-1000% or greater. Thus, if a gene exhibits a 4-fold increase in ovarian cancer tissue compared to normal tissue, a decrease of about four-fold is often desired; similarly, a 10-fold decrease in ovarian cancer tissue compared to normal tissue often provides a target value of a 10-fold increase in expression to be induced by the test compound.

35

The amount of gene expression are monitored using nucleic acid probes and the quantification of gene expression levels, or, alternatively, the gene product itself are monitored, e.g., through the use of antibodies to the ovarian cancer-associated protein and standard immunoassays. Proteomics and separation techniques may also allow
5 quantification of expression. .

In a preferred embodiment, gene expression or protein monitoring of a number of entities, i.e., an expression profile, is monitored simultaneously. Such profiles will typically involve a plurality of those entities described herein.

10 In this embodiment, the ovarian cancer nucleic acid probes are attached to biochips as outlined herein for the detection and quantification of ovarian cancer sequences in a particular cell. Alternatively, PCR are used. Thus, a series are used with dispensed primers in desired wells. A PCR reaction can then be performed and analyzed for each
15 well.

Expression monitoring are performed to identify compounds that modify the expression of one or more ovarian cancer-associated sequences, e.g., a polynucleotide sequence set out in Tables 1-3. In a preferred embodiment, a test modulator is added to the cells
20 prior to analysis. Moreover, screens are also provided to identify agents that modulate ovarian cancer, modulate ovarian cancer-associated proteins, bind to a ovarian cancer-associated protein, or interfere with the binding of a ovarian cancer-associated protein and an antibody or other binding partner.

25 The term "test compound" or "drug candidate" or "modulator" or grammatical equivalents as used herein describes any molecule, e.g., protein, oligopeptide, small organic molecule, polysaccharide, polynucleotide, etc., to be tested for the capacity to directly or indirectly alter the ovarian cancer phenotype or the expression of a ovarian cancer sequence, e.g., a nucleic acid or protein sequence. In preferred embodiments,
30 modulators alter expression profiles, or expression profile nucleic acids or proteins provided herein. In one embodiment, the modulator suppresses a ovarian cancer phenotype, e.g. to a normal tissue fingerprint. In another embodiment, a modulator induced a ovarian cancer phenotype. Generally, a plurality of assay mixtures are run in parallel with different agent concentrations to obtain a differential response to the various
35 concentrations. Typically, one of these concentrations serves as a negative control, i.e., at zero concentration or below the level of detection.

Drug candidates encompass numerous chemical classes, though typically they are organic molecules, preferably small organic compounds having a molecular weight of more than 100 and less than about 2,500 daltons. Preferred small molecules are less than 2000, or less than 1500 or less than 1000 or less than 500 Daltons. Candidate agents comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding, and typically include at least an amine, carbonyl, hydroxyl or carboxyl group, preferably at least two of the functional chemical groups. The candidate agents often comprise cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules including peptides, saccharides, fatty acids, steroids, purines, pyrimidines, derivatives, structural analogs or combinations thereof. Particularly preferred are peptides.

In one aspect, a modulator will neutralize the effect of a ovarian cancer-associated protein. By "neutralize" is meant that activity of a protein is inhibited or blocked and the consequent effect on the cell.

In certain embodiments, combinatorial libraries of potential modulators will be screened for an ability to bind to a ovarian cancer polypeptide or to modulate activity. Conventionally, new chemical entities with useful properties are generated by identifying a chemical compound (called a "lead compound") with some desirable property or activity, e.g., inhibiting activity, creating variants of the lead compound, and evaluating the property and activity of those variant compounds. Often, high throughput screening (HTS) methods are employed for such an analysis.

In one preferred embodiment, high throughput screening methods involve providing a library containing a large number of potential therapeutic compounds (candidate compounds). Such "combinatorial chemical libraries" are then screened in one or more assays to identify those library members (particular chemical species or subclasses) that display a desired characteristic activity. The compounds thus identified can serve as conventional "lead compounds" or can themselves be used as potential or actual therapeutics.

A combinatorial chemical library is a collection of diverse chemical compounds generated by either chemical synthesis or biological synthesis by combining a number of chemical

"building blocks" such as reagents. For example, a linear combinatorial chemical library, such as a polypeptide (e.g., mutein) library, is formed by combining a set of chemical building blocks called amino acids in every possible way for a given compound length (i.e., the number of amino acids in a polypeptide compound). Millions of chemical compounds are synthesized through such combinatorial mixing of chemical building blocks (Gallop *et al.*, 1994, *J. Med. Chem.* 37(9):1233-1251).

Preparation and screening of combinatorial chemical libraries is well known to those of skill in the art. Such combinatorial chemical libraries include, but are not limited to, peptide libraries, peptoids, encoded peptides, random bio-oligomers, nonpeptidal peptidomimetics, analogous organic syntheses of small compound libraries, nucleic acid libraries, peptide nucleic acid libraries, antibody libraries, carbohydrate libraries and small organic molecule libraries.

The assays to identify modulators are amenable to high throughput screening. Preferred assays thus detect enhancement or inhibition of ovarian cancer gene transcription, inhibition or enhancement of polypeptide expression, and inhibition or enhancement of polypeptide activity.

High throughput assays for the presence, absence, quantification, or other properties of particular nucleic acids or protein products are well known to those of skill in the art. Similarly, binding assays and reporter gene assays are similarly well known. Thus, e.g., U.S. Patent No. 5,559,410 discloses high throughput screening methods for proteins, U.S. Patent No. 5,585,639 discloses high throughput screening methods for nucleic acid binding (i.e., in arrays), while U.S. Patent Nos. 5,576,220 and 5,541,061 disclose high throughput methods of screening for ligand/antibody binding.

In addition, high throughput screening systems are commercially available (*see, e.g.,* Zymark Corp., Hopkinton, MA; Air Technical Industries, Mentor, OH; Beckman Instruments, Inc. Fullerton, CA; Precision Systems, Inc., Natick, MA, *etc.*). These systems typically automate entire procedures, including all sample and reagent pipetting, liquid dispensing, timed incubations, and final readings of the microplate in detectors appropriate for the assay. These configurable systems provide high throughput and rapid start up as well as a high degree of flexibility and customization. The manufacturers of such systems provide detailed protocols for various high throughput systems. Thus, e.g.,

Zymark Corp. provides technical bulletins describing screening systems for detecting the modulation of gene transcription, ligand binding, and the like.

In one embodiment, modulators are proteins, often naturally occurring proteins or
5 fragments of naturally occurring proteins. Thus, e.g., cellular extracts containing proteins, or random or directed digests of proteinaceous cellular extracts, are used. In this way libraries of proteins are made for screening in the methods of the invention. Particularly preferred in this embodiment are libraries of bacterial, fungal, viral, and mammalian proteins, with the latter being preferred, and human proteins being especially preferred.
10 Particularly useful test compound will be directed to the class of proteins to which the target belongs, e.g., substrates for enzymes or ligands and receptors.

In a preferred embodiment, modulators are peptides of from about 5 to about 30 amino acids, with from about 5 to about 20 amino acids being preferred, and from about 7 to
15 about 15 being particularly preferred. The peptides are digests of naturally occurring proteins as is outlined above, random peptides, or "biased" random peptides. By "randomized" or grammatical equivalents herein is meant that each nucleic acid and peptide consists of essentially random nucleotides and amino acids, respectively. Since generally these random peptides (or nucleic acids, discussed below) are chemically
20 synthesized, they may incorporate any nucleotide or amino acid at any position. The synthetic process are designed to generate randomized proteins or nucleic acids, to allow the formation of all or most of the possible combinations over the length of the sequence, thus forming a library of randomized candidate bioactive proteinaceous agents.

25

In one embodiment, the library is fully randomized, with no sequence preferences or constants at any position. In a preferred embodiment, the library is biased. That is, some positions within the sequence are either held constant, or are selected from a limited number of possibilities. For example, in a preferred embodiment, the nucleotides or
30 amino acid residues are randomized within a defined class, e.g., of hydrophobic amino acids, hydrophilic residues, sterically biased (either small or large) residues, towards the creation of nucleic acid binding domains, the creation of cysteines, for cross-linking, prolines for SH-3 domains, serines, threonines, tyrosines or histidines for phosphorylation sites, etc., or to purines, etc.

35

Modulators of ovarian cancer can also be nucleic acids, as defined below. As described above generally for proteins, nucleic acid modulating agents are naturally occurring nucleic acids, random nucleic acids, or "biased" random nucleic acids. For example, digests of procaryotic or eucaryotic genomes are used as is outlined above for proteins.

5

In certain embodiments, the activity of a ovarian cancer-associated protein is down-regulated, or entirely inhibited, by the use of antisense polynucleotide, *i.e.*, a nucleic acid complementary to, and which can preferably hybridize specifically to, a coding mRNA nucleic acid sequence, *e.g.*, a ovarian cancer-associated protein mRNA, or a subsequence thereof. Binding of the antisense polynucleotide to the mRNA reduces the translation and/or stability of the mRNA.

10

In the context of this invention, antisense polynucleotides can comprise naturally-occurring nucleotides, or synthetic species formed from naturally-occurring subunits or their close homologs. Antisense polynucleotides may also have altered sugar moieties or inter-sugar linkages. Exemplary among these are the phosphorothioate and other sulfur containing species which are known for use in the art. Analogs are comprehended by this invention so long as they function effectively to hybridize with the ovarian cancer-associated protein mRNA. See, *e.g.*, Isis Pharmaceuticals, Carlsbad, CA; Sequitor, Inc., Natick, MA.

15

20

Such antisense polynucleotides can readily be synthesized using recombinant means, or are synthesized *in vitro*. Equipment for such synthesis is sold by several vendors, including Applied Biosystems. The preparation of other oligonucleotides such as phosphorothioates and alkylated derivatives is also well known to those of skill in the art.

25

Antisense molecules as used herein include antisense or sense oligonucleotides. Sense oligonucleotides can, *e.g.*, be employed to block transcription by binding to the anti-sense strand. The antisense and sense oligonucleotide comprise a single-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target mRNA (sense) or DNA (antisense) sequences for ovarian cancer molecules. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment generally at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, *e.g.*, Stein & Cohen (*Cancer Res.* 48:2659 (1988) and van der Krol *et al.* (*BioTechniques* 6:958 (1988)).

30

35

- In addition to antisense polynucleotides, ribozymes are used to target and inhibit transcription of ovarian cancer-associated nucleotide sequences. A ribozyme is an RNA molecule that catalytically cleaves other RNA molecules. Different kinds of ribozymes have been described, including group I ribozymes, hammerhead ribozymes, hairpin ribozymes, RNase P, and axhead ribozymes (see, e.g., Castanotto *et al.*, *Adv. in Pharmacology* 25: 289-317 (1994) for a general review of the properties of different ribozymes).
- Methods of preparing ribozymes are well known to those of skill in the art (see, e.g., WO 94/26877; Ojwang *et al.*, *Proc. Natl. Acad. Sci. USA* 90:6340-6344 (1993); Yamada *et al.*, *Human Gene Therapy* 1:39-45 (1994); Leavitt *et al.*, *Proc. Natl. Acad. Sci. USA* 92:699- 703 (1995); Leavitt *et al.*, *Human Gene Therapy* 5:1151-120 (1994); and Yamada *et al.*, *Virology* 205: 121-126 (1994)).
- Polynucleotide modulators of ovarian cancer are introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind to its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell. Alternatively, a polynucleotide modulator of ovarian cancer are introduced into a cell containing the target nucleic acid sequence, e.g., by formation of an polynucleotide-lipid complex, as described in WO 90/10448. It is understood that the use of antisense molecules or knock out and knock in models may also be used in screening assays as discussed above, in addition to methods of treatment.
- As noted above, gene expression monitoring is conveniently used to test candidate modulators (e.g., protein, nucleic acid or small molecule). After the candidate agent has been added and the cells allowed to incubate for some period of time, the sample containing a target sequence to be analyzed is added to the biochip. If required, the target sequence is prepared using known techniques. For example, the sample are treated to lyse the cells, using known lysis buffers, electroporation, etc., with purification and/or amplification such as PCR performed as appropriate. For example, an *in vitro*

transcription with labels covalently attached to the nucleotides is performed. Generally, the nucleic acids are labeled with biotin-FITC or PE, or with cy3 or cy5.

5 In a preferred embodiment, the target sequence is labeled with, e.g., a fluorescent, a chemiluminescent, a chemical, or a radioactive signal, to provide a means of detecting the target sequence's specific binding to a probe. The label also are an enzyme, such as, alkaline phosphatase or horseradish peroxidase, which when provided with an appropriate substrate produces a product that are detected. Alternatively, the label are a labeled compound or small molecule, such as an enzyme inhibitor, that binds but is not
10 catalyzed or altered by the enzyme. The label also are a moiety or compound, such as, an epitope tag or biotin which specifically binds to streptavidin. For the example of biotin, the streptavidin is labeled as described above, thereby, providing a detectable signal for the bound target sequence. Unbound labeled streptavidin is typically removed prior to analysis.

15 As will be appreciated by those in the art, these assays are direct hybridization assays or can comprise "sandwich assays", which include the use of multiple probes, as is generally outlined in U.S. Patent Nos. 5,681,702, 5,597,909, 5,545,730, 5,594,117, 5,591,584, 5,571,670, 5,580,731, 5,571,670, 5,591,584, 5,624,802, 5,635,352,
20 5,594,118, 5,359,100, 5,124,246 and 5,681,697, all of which are hereby incorporated by reference. In this embodiment, in general, the target nucleic acid is prepared as outlined above, and then added to the biochip comprising a plurality of nucleic acid probes, under conditions that allow the formation of a hybridization complex.

25 A variety of hybridization conditions are used in the present invention, including high, moderate and low stringency conditions as outlined above. The assays are generally run under stringency conditions which allows formation of the label probe hybridization complex only in the presence of target. Stringency are controlled by altering a step parameter that is a thermodynamic variable, including, but not limited to, temperature,
30 formamide concentration, salt concentration, chaotropic salt concentration pH, organic solvent concentration, etc.

These parameters may also be used to control non-specific binding, as is generally outlined in U.S. Patent No. 5,681,697. Thus it are desirable to perform certain steps at
35 higher stringency conditions to reduce non-specific binding.

The reactions outlined herein are accomplished in a variety of ways. Components of the reaction are added simultaneously, or sequentially, in different orders, with preferred embodiments outlined below. In addition, the reaction may include a variety of other reagents. These include salts, buffers, neutral proteins, e.g. albumin, detergents, *etc.* which are used to facilitate optimal hybridization and detection, and/or reduce non-specific or background interactions. Reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, *etc.*, may also be used as appropriate, depending on the sample preparation methods and purity of the target.

The assay data are analyzed to determine the expression levels, and changes in expression levels as between states, of individual genes, forming a gene expression profile.

Screens are performed to identify modulators of the ovarian cancer phenotype. In one embodiment, screening is performed to identify modulators that can induce or suppress a particular expression profile, thus preferably generating the associated phenotype. In another embodiment, e.g., for diagnostic applications, having identified differentially expressed genes important in a particular state, screens are performed to identify modulators that alter expression of individual genes. In another embodiment, screening is performed to identify modulators that alter a biological function of the expression product of a differentially expressed gene. Again, having identified the importance of a gene in a particular state, screens are performed to identify agents that bind and/or modulate the biological activity of the gene product.

In addition screens are done for genes that are induced in response to a candidate agent. After identifying a modulator based upon its ability to suppress a ovarian cancer expression pattern leading to a normal expression pattern, or to modulate a single ovarian cancer gene expression profile so as to mimic the expression of the gene from normal tissue, a screen as described above are performed to identify genes that are specifically modulated in response to the agent. Comparing expression profiles between normal tissue and agent treated ovarian cancer tissue reveals genes that are not expressed in normal tissue or ovarian cancer tissue, but are expressed in agent treated tissue. These agent-specific sequences are identified and used by methods described herein for ovarian cancer genes or proteins. In particular these sequences and the proteins they encode find use in marking or identifying agent treated cells. In addition,

antibodies are raised against the agent induced proteins and used to target novel therapeutics to the treated ovarian cancer tissue sample.

Thus, in one embodiment, a test compound is administered to a population of ovarian cancer cells, that have an associated ovarian cancer expression profile. By "administration" or "contacting" herein is meant that the candidate agent is added to the cells in such a manner as to allow the agent to act upon the cell, whether by uptake and intracellular action, or by action at the cell surface. In some embodiments, nucleic acid encoding a proteinaceous candidate agent (i.e., a peptide) are put into a viral construct such as an adenoviral or retroviral construct, and added to the cell, such that expression of the peptide agent is accomplished. Regulatable gene administration systems can also be used.

Once the test compound has been administered to the cells, the cells are washed if desired and are allowed to incubate under preferably physiological conditions for some period of time. The cells are then harvested and a new gene expression profile is generated, as outlined herein.

Thus, e.g., ovarian cancer tissue are screened for agents that modulate, e.g., induce or suppress the ovarian cancer phenotype. A change in at least one gene, preferably many, of the expression profile indicates that the agent has an effect on ovarian cancer activity. By defining such a signature for the ovarian cancer phenotype, screens for new drugs that alter the phenotype are devised. With this approach, the drug target need not be known and need not be represented in the original expression screening platform, nor does the level of transcript for the target protein need to change.

In a preferred embodiment, as outlined above, screens are done on individual genes and gene products (proteins). That is, having identified a particular differentially expressed gene as important in a particular state, screening of modulators of either the expression of the gene or the gene product itself are done. The gene products of differentially expressed genes are sometimes referred to herein as "ovarian cancer-associated proteins" or a "ovarian cancer modulatory protein". The ovarian cancer modulatory protein are a fragment, or alternatively, be the full length protein to the fragment encoded by the nucleic acids referred to in Tables 1-3. Preferably, the ovarian cancer modulatory protein is a fragment. In a preferred embodiment, the ovarian cancer amino acid sequence which is used to determine sequence identity or similarity is encoded by a

nucleic acid referred to in Tables 1-3. In another embodiment, the sequences are naturally occurring allelic variants of a protein encoded by a nucleic acid referred to in Tables 1-3. In another embodiment, the sequences are sequence variants as further described herein.

5

Preferably, the ovarian cancer modulatory protein is a fragment of approximately 14 to 24 amino acids long. More preferably the fragment is a soluble fragment. Preferably, the fragment includes a non-transmembrane region. In a preferred embodiment, the fragment has an N-terminal Cys to aid in solubility. In one embodiment, the C-terminus of the fragment is kept as a free acid and the N-terminus is a free amine to aid in coupling, i.e., to cysteine.

10

In one embodiment the ovarian cancer-associated proteins are conjugated to an immunogenic agent as discussed herein. In one embodiment the ovarian cancer-associated protein is conjugated to BSA.

15

Measurements of ovarian cancer polypeptide activity, or of ovarian cancer or the ovarian cancer phenotype are performed using a variety of assays. For example, the effects of the test compounds upon the function of the ovarian cancer polypeptides are measured by examining parameters described above. A suitable physiological change that affects activity are used to assess the influence of a test compound on the polypeptides of this invention. When the functional consequences are determined using intact cells or animals, one can also measure a variety of effects such as, in the case of ovarian cancer associated with tumours, tumour growth, tumour metastasis, neovascularization, hormone release, transcriptional changes to both known and uncharacterized genetic markers (e.g., northern blots), changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as cGMP. In tire assays of the invention, mammalian ovarian cancer polypeptide is typically used, e.g., mouse, preferably human.

20

25

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Assays to identify compounds with modulating activity are performed *in vitro*. For example, a ovarian cancer polypeptide is first contacted with a potential modulator and incubated for a suitable amount of time, e.g., from 0.5 to 48 hours. In one embodiment, the ovarian cancer polypeptide levels are determined *in vitro* by measuring the level of protein or mRNA. The level of protein is measured using immunoassays such as western blotting, ELISA and the like with an antibody that selectively binds to the ovarian cancer

35

polypeptide or a fragment thereof. For measurement of mRNA, amplification, e.g., using PCR, LCR, or hybridization assays, e.g., northern hybridization, RNase protection, dot blotting, are preferred. The level of protein or mRNA is detected using directly or indirectly labeled detection agents, e.g., fluorescently or radioactively labeled nucleic acids, radioactively or enzymatically labeled antibodies, and the like, as described herein.

Alternatively, a reporter gene system are devised using the ovarian cancer-associated protein promoter operably linked to a reporter gene such as luciferase, green fluorescent protein, CAT, or (beta-gal. The reporter construct is typically transfected into a cell. After treatment with a potential modulator, the amount of reporter gene transcription, translation, or activity is measured according to standard techniques known to those of skill in the art.

In a preferred embodiment, as outlined above, screens are done on individual genes and gene products (proteins). That is, having identified a particular differentially expressed gene as important in a particular state, screening of modulators of the expression of the gene or the gene product itself are done. The gene products of differentially expressed genes are sometimes referred to herein as "ovarian cancer-associated proteins." The ovarian cancer-associated protein are a fragment, or alternatively, be the full length protein to a fragment shown herein.

In one embodiment, screening for modulators of expression of specific genes is performed. Typically, the expression of only one or a few genes are evaluated. In another embodiment, screens are designed to first find compounds that bind to differentially expressed proteins. These compounds are then evaluated for the ability to modulate differentially expressed activity. Moreover, once initial candidate compounds are identified, variants are further screened to better evaluate structure activity relationships.

In a preferred embodiment, binding assays are done. In general, purified or isolated gene product is used; that is, the gene products of one or more differentially expressed nucleic acids are made. For example, antibodies are generated to the protein gene products, and standard immunoassays are run to determine the amount of protein present. Alternatively, cells comprising the ovarian cancer-associated proteins are used in the assays.

Thus, in a preferred embodiment, the methods comprise combining a ovarian cancer-associated protein and a candidate compound, and determining the binding of the compound to the ovarian cancer-associated protein. Preferred embodiments utilize the human ovarian cancer-associated protein, although other mammalian proteins may also
5 be used, e.g. for the development of animal models of human disease. In some embodiments, as outlined herein, variant or derivative ovarian cancer-associated proteins are used.

Generally, in a preferred embodiment of the methods herein, the ovarian cancer-associated protein or the candidate agent is non-diffusably bound to an insoluble support
10 having isolated sample receiving areas (e.g. a microtiter plate, an array, etc.). The insoluble supports are made of any composition to which the compositions are bound, is readily separated from soluble material, and is otherwise compatible with the overall method of screening. The surface of such supports are solid or porous and of any
15 convenient shape. Examples of suitable insoluble supports include microtiter plates, arrays, membranes and beads. These are typically made of glass, plastic (e.g., polystyrene), polysaccharides, nylon or nitrocellulose, teflon™, etc. microtitre plates and arrays are especially convenient because a large number of assays are carried out simultaneously, using small amounts of reagents and samples. The particular manner of
20 binding of the composition is not crucial so long as it is compatible with the reagents and overall methods of the invention, maintains the activity of the composition and is nondiffusable. Preferred methods of binding include the use of antibodies (which do not sterically block either the ligand binding site or activation sequence when the protein is bound to the support), direct binding to "sticky" or ionic supports, chemical crosslinking,
25 the synthesis of the protein or agent on the surface, etc. Following binding of the protein or agent, excess unbound material is removed by washing. The sample receiving areas may then be blocked through incubation with bovine serum albumin (BSA), casein or other innocuous protein or other moiety.

30 In a preferred embodiment, the ovarian cancer-associated protein is bound to the support, and a test compound is added to the assay. Alternatively, the candidate agent is bound to the support and the ovarian cancer-associated protein is added. Novel binding agents include specific antibodies, non-natural binding agents identified in screens of chemical libraries, peptide analogs, etc. Of particular interest are screening assays for
35 agents that have a low toxicity for human cells. A wide variety of assays are used for this purpose, including labeled in vitro protein-protein binding assays, electrophoretic mobility

shift assays, immunoassays for protein binding, functional assays (phosphorylation assays, etc.) and the like.

5 The determination of the binding of the test modulating compound to the ovarian cancer-associated protein are done in a number of ways. In a preferred embodiment, the compound is labeled, and binding determined directly, e.g., by attaching all or a portion of the ovarian cancer-associated protein to a solid support, adding a labeled candidate agent (e.g., a fluorescent label), washing off excess reagent, and determining whether the label is present on the solid support. Various blocking and washing steps are utilized
10 as appropriate.

In some embodiments, only one of the components is labeled, e.g., the proteins (or proteinaceous candidate compounds) are labeled. Alternatively, more than one component are labeled with different labels, e.g., ^{125}I for the proteins and a fluorophor for
15 the compound. Proximity reagents, e.g., quenching or energy transfer reagents are also useful.

In one embodiment, the binding of the test compound is determined by competitive binding assay. The competitor is a binding moiety known to bind to the target molecule
20 (i.e., a ovarian cancer-associated protein), such as an antibody, peptide, binding partner, ligand, etc. Under certain circumstances, there are competitive binding between the compound and the binding moiety, with the binding moiety displacing the compound. In one embodiment, the test compound is labeled. Either the compound, or the competitor, or both, is added first to the protein for a time sufficient to allow binding, if present.
25 Incubations are performed at a temperature which facilitates optimal activity, typically between 4 and 40°C. Incubation periods are typically optimized, e.g., to facilitate rapid high throughput screening. Typically between 0.1 and 1 hour will be sufficient. Excess reagent is generally removed or washed away. The second component is then added, and the presence or absence of the labeled component is followed, to indicate binding.

30 In a preferred embodiment, the competitor is added first, followed by the test compound. Displacement of the competitor is an indication that the test compound is binding to the ovarian cancer-associated protein and thus is capable of binding to, and potentially modulating, the activity of the ovarian cancer-associated protein. In this embodiment,
35 either component are labeled. Thus, e.g., if the competitor is labeled, the presence of

label in the wash solution indicates displacement by the agent. Alternatively, if the test compound is labeled, the presence of the label on the support indicates displacement.

5 In an alternative preferred embodiment, the test compound is added first, with incubation and washing, followed by the competitor. The absence of binding by the competitor may indicate that the test compound is bound to the ovarian cancer-associated protein with a higher affinity. Thus, if the test compound is labeled, the presence of the label on the support, coupled with a lack of competitor binding, may indicate that the test compound is capable of binding to the ovarian cancer-associated protein.

10 In a preferred embodiment, the methods comprise differential screening to identify agents that are capable of modulating the activity of the ovarian cancer-associated proteins. In this embodiment, the methods comprise combining a ovarian cancer-associated protein and a competitor in a first sample. A second sample comprises a test
15 compound, a ovarian cancer-associated protein, and a competitor. The binding of the competitor is determined for both samples, and a change, or difference in binding between the two samples indicates the presence of an agent capable of binding to the ovarian cancer-associated protein and potentially modulating its activity. That is, if the binding of the competitor is different in the second sample relative to the first sample, the
20 agent is capable of binding to the ovarian cancer-associated protein.

Alternatively, differential screening is used to identify drug candidates that bind to the native ovarian cancer-associated protein, but cannot bind to modified ovarian cancer-associated proteins. The structure of the ovarian cancer-associated protein are modeled,
25 and used in rational drug design to synthesize agents that interact with that site. Drug candidates that affect the activity of a ovarian cancer-associated protein are also identified by screening drugs for the ability to either enhance or reduce the activity of the protein.

30 Positive controls and negative controls are used in the assays. Preferably control and test samples are performed in at least triplicate to obtain statistically significant results. Incubation of all samples is for a time sufficient for the binding of the agent to the protein. Following incubation, samples are washed free of non-specifically bound material and the amount of bound, generally labeled agent determined. For example, where a
35 radiolabel is employed, the samples are counted in a scintillation counter to determine the amount of bound compound.

A variety of other reagents are included in the screening assays. These include reagents like salts, neutral proteins, e.g. albumin, detergents, etc. which are used to facilitate optimal protein-protein binding and/or reduce non-specific or background interactions.

5 Also reagents that otherwise improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, anti-microbial agents, etc., are used. The mixture of components are added in an order that provides for the requisite binding.

10 In a preferred embodiment, the invention provides methods for screening for a compound capable of modulating the activity of a ovarian cancer-associated protein. The methods comprise adding a test compound, as defined above, to a cell comprising ovarian cancer-associated proteins. Preferred cell types include almost any cell. The cells contain a recombinant nucleic acid that encodes a ovarian cancer-associated protein. In a preferred embodiment, a library of candidate agents are tested on a plurality of cells.

15 In one aspect, the assays are evaluated in the presence or absence or previous or subsequent exposure of physiological signals, e.g. hormones, antibodies, peptides, antigens, cytokines, growth factors, action potentials, pharmacological agents including chemotherapeutics, radiation, carcinogenics, or other cells (i.e. cell-cell contacts). In another example, the determinations are determined at different stages of the cell cycle process.

20 In this way, compounds that modulate ovarian cancer agents are identified. Compounds with pharmacological activity are able to enhance or interfere with the activity of the ovarian cancer-associated protein. Once identified, similar structures are evaluated to identify critical structural feature of the compound.

30 In one embodiment, a method of inhibiting ovarian cancer cell division is provided. The method comprises administration of a ovarian cancer inhibitor. In another embodiment, a method of inhibiting ovarian cancer is provided. The method comprises administration of a ovarian cancer inhibitor. In a further embodiment, methods of treating cells or individuals with ovarian cancer are provided. The method comprises administration of a ovarian cancer inhibitor.

35 In one embodiment, a ovarian cancer inhibitor is an antibody as discussed above. In another embodiment, the ovarian cancer inhibitor is an antisense molecule.

A variety of cell growth, proliferation, and metastasis assays are known to those of skill in the art, as described below.

5 *Soft agar growth or colony formation in suspension*

Normal cells require a solid substrate to attach and grow. When the cells are transformed, they lose this phenotype and grow detached from the substrate. For example, transformed cells can grow in stirred suspension culture or suspended in semi-solid media, such as semi-solid or soft agar. The transformed cells, when
10 transfected with tumour suppressor genes, regenerate normal phenotype and require a solid substrate to attach and grow. Soft agar growth or colony formation in suspension assays are used to identify modulators of ovarian cancer sequences, which when expressed in host cells, inhibit abnormal cellular proliferation and transformation. A therapeutic compound would reduce or eliminate the host cells' ability to grow in stirred
15 suspension culture or suspended in semisolid media, such as semi-solid or soft.

Techniques for soft agar growth or colony formation in suspension assays are described in Freshney, *Culture of Animal Cells a Manual of Basic Technique* (3rd ed., 1994), herein incorporated by reference. See also, the methods section of Garkavtsev *et al.* (1996),
20 supra, herein incorporated by reference.

Contact inhibition and density limitation of growth

Normal cells typically grow in a flat and organized pattern in a petri dish until they touch other cells. When the cells touch one another, they are contact inhibited and stop
25 growing. When cells are transformed, however, the cells are not contact inhibited and continue to grow to high densities in disorganized foci. Thus, the transformed cells grow to a higher saturation density than normal cells. This are detected morphologically by the formation of a disoriented monolayer of cells or rounded cells in foci within the regular pattern of normal surrounding cells. Alternatively, labeling index with (³H)-thymidine at
30 saturation density are used to measure density limitation of growth. See Freshney (1994), supra. The transformed cells, when transfected with tumour suppressor genes, regenerate a normal phenotype and become contact inhibited and would grow to a lower density.

35 In this assay, labeling index with (³H)-thymidine at saturation density is a preferred method of measuring density limitation of growth. Transformed host cells are transfected

with a ovarian cancer-associated sequence and are grown for 24 hours at saturation density in non-limiting medium conditions. The percentage of cells labeling with (³H)-thymidine is determined autoradiographically. See, Freshney (1994), *supra*.

5 *Growth factor or serum dependence*

Transformed cells have a lower serum dependence than their normal counterparts (see, e.g., Temin, J. *Natl. Cancer Inst.* 37:167-175 (1966); Eagle *et al.*, J. *Exp. Med.* 131:836-879 (1970)); Freshney, *supra*. This is in part due to release of various growth factors by the transformed cells. Growth factor or serum dependence of transformed host
10 cells are compared with that of control. *Tumor specific markers levels* Tumor cells release an increased amount of certain factors (hereinafter "tumour specific markers") than their normal counterparts. For example, plasminogen activator (PA) is released from human glioma at a higher level than from normal brain cells (see, e.g., Gullino, *Angiogenesis, tumour vascularization, and potential interference with tumour growth*. in
15 *Biological Responses in Cancer*, pp. 178-184 (Mihich (ed.) 1985)). Similarly, Tumor angiogenesis factor (TAF) is released at a higher level in tumour cells than their normal counterparts. See, e.g., Folkman, *Angiogenesis and Cancer*, *Sem Cancer Biol.* (1992)). Various techniques which measure the release of these factors are described in Freshney (1994), *supra*. Also, see, Unkless *et al.*, J. *Biol. Chem.* 249:4295-4305 (1974);
20 Strickland & Beers, J. *Biol. Chem.* 251:5694-5702 (1976); Whur *et al.*, *Br. J. Cancer* 42:305 312 (1980); Gullino, *Angiogenesis, tumour vascularization, and potential interference with tumour growth*. in *Biological Responses in Cancer*, pp. 178-184 (Mihich (ed.) 1985); Freshney *Anticancer Res.* 5:111-130 (1985).

25 *Invasiveness into Matrigel*

The degree of invasiveness into Matrigel or some other extracellular matrix constituent are used as an assay to identify compounds that modulate ovarian cancer-associated sequences. Tumor cells exhibit a good correlation between malignancy and invasiveness of cells into Matrigel or some other extracellular matrix constituent. In this assay,
30 tumourigenic cells are typically used as host cells. Expression of a tumour suppressor gene in these host cells would decrease invasiveness of the host cells.

Techniques described in Freshney (1994), *supra*, are used. Briefly, the level of invasion of host cells are measured by using filters coated with Matrigel or some other
35 extracellular matrix constituent. Penetration into the gel, or through to the distal side of the filter, is rated as invasiveness, and rated histologically by number of cells and

distance moved, or by prelabeling the cells with ^{125}I and counting the radioactivity on the distal side of the filter or bottom of the dish. See, e.g., Freshney (1984), *supra*.

Tumor growth in vivo

- 5 Effects of ovarian cancer-associated sequences on cell growth are tested in transgenic or immune-suppressed mice. Knock-out transgenic mice are made, in which the ovarian cancer gene is disrupted or in which a ovarian cancer gene is inserted. Knock- out transgenic mice are made by insertion of a marker gene or other heterologous gene into the endogenous ovarian cancer gene site in the mouse genome via homologous recombination. Such mice can also be made by substituting the endogenous ovarian cancer gene with a mutated version of the ovarian cancer gene, or by mutating the endogenous ovarian cancer gene, e.g., by exposure to carcinogens.

- 15 A DNA construct is introduced into the nuclei of embryonic stem cells. Cells containing the newly engineered genetic lesion are injected into a host mouse embryo, which is re-implanted into a recipient female. Some of these embryos develop into chimeric mice that possess germ cells partially derived from the mutant cell line. Therefore, by breeding the chimeric mice it is possible to obtain a new line of mice containing the introduced genetic lesion (see, e.g., Capecchi *et al.*, *Science* 244:1288 (1989)). Chimeric targeted mice are derived according to Hogan *et al.*, *Manipulating the Mouse Embryo: A Laboratory Manual*, Cold Spring Harbor Laboratory (1988) and *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, ed., IRL Press, Washington, D.C., (1987).

- 25 Alternatively, various immune-suppressed or immune-deficient host animals are used. For example, genetically athymic "nude" mouse (see, e.g., Giovanella *et al.*, *J. Natl. Cancer Inst.* 52:921 (1974)), a SCID mouse, a thymectomized mouse, or an irradiated mouse (see, e.g., Bradley *et al.*, *Br. J. Cancer* 38:263 (1978); Selby *et al.*, *Br. J. Cancer* 41:52 (1980)) are used as a host. Transplantable tumour cells (typically about 10^6 cells) injected into isogenic hosts will produce invasive tumours in a high proportions of cases, while normal cells of similar origin will not. In hosts which developed invasive tumours, cells expressing a ovarian cancer-associated sequences are injected subcutaneously. After a suitable length of time, preferably 4 to 8 weeks, tumour growth is measured (e.g. by volume or by its two largest dimensions) and compared to the control. Tumours that have a statistically significant reduction (using, e.g. Student's T test) are said to have inhibited growth.

Administration

therapeutic reagents of the invention are administered to patients, therapeutically. Typically, such proteins/polynucleotides and substances may preferably be combined
5 with various components to produce compositions of the invention. Preferably the compositions are combined with a pharmaceutically acceptable carrier or diluent to produce a pharmaceutical composition (which are for human or animal use). Suitable carriers and diluents include isotonic saline solutions, for example phosphate-buffered saline. The composition of the invention are administered by direct injection. The
10 composition are formulated for parenteral, intramuscular, intravenous, subcutaneous, intraocular, oral, vaginal or transdermal administration. Typically, each protein are administered at a dose of from 0.01 to 30 mg/kg body weight, preferably from 0.1 to 10 mg/kg, more preferably from 0.1 to 1 mg/kg body weight.

15 Polynucleotides/vectors encoding polypeptide components for use in modulating the activity of the ovarian cancer-associated proteins/polynucleotides are administered directly as a naked nucleic acid construct. When the polynucleotides/vectors are administered as a naked nucleic acid, the amount of nucleic acid administered may typically be in the range of from 1 µg to 10 mg, preferably from 100 µg to 1 mg.

20

Uptake of naked nucleic acid constructs by mammalian cells is enhanced by several known transfection techniques for example those including the use of transfection agents. Example of these agents include cationic agents (for example calcium phosphate and DEAE-dextran) and lipofectants (for example lipofectamTM and transfectamTM).
25 Typically, nucleic acid constructs are mixed with the transfection agent to produce a composition.

Preferably the polynucleotide or vector of the invention is combined with a pharmaceutically acceptable carrier or diluent to produce a pharmaceutical composition.
30 Suitable carriers and diluents include isotonic saline solutions, for example phosphate-buffered saline. The composition are formulated for parenteral, intramuscular, intravenous, subcutaneous, oral, intraocular or transdermal administration.

The pharmaceutical compositions are administered in a range of unit dosage forms
35 depending on the method of administration. For example, unit dosage forms suitable for oral administration include, powder, tablets, pills, capsules and lozenges. Orally

administered dosage forms will typically be formulated to protect the active ingredient from digestion and may therefore be complexed with appropriate carrier molecules and/or packaged in an appropriately resistant carrier. Suitable carrier molecules and packaging materials/barrier materials are known in the art.

5

The compositions of the invention are administered for therapeutic or prophylactic treatments. In therapeutic applications, compositions are administered to a patient suffering from a disease (e.g. ovarian cancer) in an amount sufficient to cure or at least partially ameliorate the disease and its complications. An amount adequate to accomplish this is defined as a "therapeutically effective dose". An amount of the composition that is capable of preventing or slowing the development of cancer in a patient is referred to as a "prophylactically effective dose".

10

The routes of administration and dosages described are intended only as a guide since a skilled practitioner will be able to determine readily the optimum route of administration and dosage for any particular patient and condition.

15

The present invention is further described with reference to the accompanying drawings and the following non-limiting examples.

20

EXAMPLE 1

*Gene expression profiling to identify differentially-expressed
genes in ovarian cancer*

1. Tissue Bank and Database

5 Tissue was collected from patients undergoing treatment at the GCC, we have established
an Ovarian Cancer Tissue Bank and Clinical Database that currently holds data on over
400 cases treated at the GCC between 1986 and 2002. Tissue (currently 149 fresh/frozen
and 292 archival fixed paraffin-embedded samples) was acquired from patients undergoing
10 cytoreductive surgery and does not interfere with the collection of tissue for the normal
processing of diagnostic specimens. Patient consent, included in all our studies, was
collected prior to surgery. Tissue specimens and their associated pathology reports were
coded in order to maintain patient confidentiality. Uncoded data was electronically and/or
physically locked with restricted access by appropriate senior investigators only. Clinical
(diagnosis, treatment, residual disease) and pathological data (tumour grade, stage) were
15 collected and updated (disease recurrence, patient survival) at regular intervals. This study
has ethical approval from the South Eastern Sydney Area Health Service Research Ethics
Committee, Australia. Clinical data and tissue collection are ongoing.

2. Genetic profiling of ovarian cancers

20 In order to identify those genes differentially regulated in epithelial ovarian cancer 51
ovarian cancer tumor samples were manually dissected from biological samples derived
from subjects undergoing cytoreductive surgery. These samples comprised 8
endometrioid tumors, 4 mucinous tumors and 31 serous epithelial ovarian tumors, 12
corresponding omental deposits and 8 borderline (low-malignant potential) tumors.

25

RNA was isolated from the tumor samples in addition to 4 normal ovary samples using
Trizol reagent (Life Technologies, Rockville, MD, USA) essentially according to
manufacturer's instructions. RNA was then reverse transcribed using an oligo(dT)
anchored oligonucleotide that additionally comprised a T7 promoter sequence. Isolated
30 cDNA was then transcribed *in vitro* using the T7 MEGAscript kit (Ambion, Austin, TX,
USA) according to manufacturer's instructions. Transcription was performed with
biotinylated nucleotides (Bio-11-CTP and Bio-16-UTP) to enable detection of the
transcribed cRNA.

35 Levels of gene expression in the cancer samples was then determined by analysing the
transcribed cDNA samples using customized Affymetrix GeneChip® microarrays that

comprise 59,618 oligonucleotide probe sets. These probe sets facilitate analysis of 46,000 gene clusters, representing over 90% of the predicted expressed human genome.

5 Data were normalized, and changes in gene expression detected using a ranked penalized t-statistic with p-values adjusted for multiple testing using the Holm procedure. Analysis was performed using the LIMMA package (available from Bioconductor, Biostatistics Unit of the Dana Farber Cancer Institute at the Harvard Medical School/Harvard School of Public Health).

10 Gene expression in 186 samples representing 52 different tissues of the body was also determined using the previously described methods to facilitate the identification of changes in gene expression that are specific for ovarian cancer.

15 Using this method 284 up-regulated transcripts and 186 down-regulated transcripts were identified.

In order to determine the efficacy of such a method of analysis for determining gene expression changes associated with ovarian cancer, those genes identified were compared to results of published expression profile studies. Using this method, 71
20 genes were identified in the present study that had been previously identified, including, for example, genes known to be over-expressed in ovarian cancer, such as, for example MUC1 and E-cadherin.

The ovarian cancer-associated genes and proteins set forth in Table 1 include
25 sequences that are up-regulated or down-regulated in ovarian cancer subjects, including subjects suffering specifically from serous, endometrioid, mucinous or clear cell ovarian cancer, or non-invasive (borderline) ovarian cancers of any phenotype, and subjects that suffered from recurrences of ovarian cancer in the medium term, or died within the medium term.

30 Data presented in Table 2 indicate those genes that are expressed at significantly higher levels or significantly reduced levels in patients suffering from serous cancer relative to the level of expression of the same genes in a normal or healthy subject.

EXAMPLE 2*Validation of gene expression profiling results using tissue microarrays*

Each of the transcripts identified as being differentially-expressed specifically in ovarian cancer was then further analysed using *in situ* hybridization or immunohistochemical staining of tissue microarrays constructed from a large cohort of primary ovarian tumor tissue. Such analysis confirms upregulation, down-regulation or total loss of expression of the transcripts identified in the microarray analysis of tumor samples.

Furthermore, as each of the samples in the tissue microarray have been clinicopathologically characterized (for example to identify cancer grade and/or disease stage) and the subjects from whom the tumors were isolated continuously monitored (to detect for example, death or relapse of cancer), changes with gene expression were also analysed for correlation with such parameters in order to determine predictive changes in gene expression.

The relative intensity and percentage of cells staining was determined and evaluated for associations with clinical stage and grade of disease and disease relapse using the Kaplan Meier method and log-rank test, and by univariate and bivariate analyses in a Cox proportional hazards model for gene expression and other clinical and pathologic predictors of outcome to determine the potential independent prognostic value of the markers being assessed.

Immunohistochemical analysis has been performed on several genes identified in gene profiling analysis of ovarian cancer samples. For example, SOX17, Ep-CAM and claudin 3 were shown by gene profiling analysis to be specifically up-regulated in ovarian cancer compared to normal ovaries (Figure 1 and Figure 2). Using immunohistochemical analysis, it was determined that SOX17, Ep-CAM and claudin 3 are upregulated in serous cancer, mucinous cancer, endometrioid cancer and clear cell ovarian cancer.

Furthermore, immunohistochemical analysis has been used to analyse the expression of several other genes that are specifically upregulated in mucinous ovarian cancer. In particular the expression of LI-cadherin (cadherin 17), meprin alpha and Galectin 4 as detected using immunohistochemistry is shown in Figure 3. There was a significant increase in protein detected in the mucinous ovarian cancer samples compared to the normal ovary sample and serous ovarian cancer sample.

Immunohistochemical analysis was also performed to analyse the expression of three genes that are known to be upregulated in ovarian cancer (CA125, MUC-1 and E-cadherin) (Figures 1 and 2).

5

EXAMPLE 3

Identification of prognostic markers of ovarian cancer

Using a classical survival analysis to mine expression profiling data several genes that are associated with poor patient outcome (ie death or cancer relapse) have been identified (Tables 2 and 3). Such genes have clinical utility as prognostic indicators of disease. .

10

Using detailed clinicopathological and postoperative data on all of the 51 patients included in our transcriptional profiling studies, including details of biochemical (eg. rising serum CA-125) and/or clinical recurrence of disease and overall survival, expression profiles were correlates with clinical parameters.

15

A preliminary survival analysis was performed on the 33 serous cancers within this cohort. The median follow-up time for these patients was 25.5 months from the date of primary laparotomy to the date of last follow-up or the date of death, and 21 of these patients (66%) were deceased from causes related to their malignancy.

20

Preliminary analysis of the expression profiles of these tumors identified several potential gene clusters that were associated with an increased risk of biochemical and clinical recurrence and overall survival, including the *EDD* gene (SEQ ID NO: 63). Exemplary prognostic markers for detecting ovarian cancer are shown in Tables 1 and 3. Preferred markers are indicated in Table 3.

25

Using immunohistochemical analysis two genes have been confirmed to be upregulated in serous ovarian cancer. In particular, sFRP4, a negative signalling protein of the Wnt pathway, and SOCS3, a negative signaller of IL-6 induced signalling are specifically upregulated in serous ovarian cancer when compared to normal ovarian tissue (Figure 4A).

30

Furthermore, using clinical patient data and correlating this information with gene expression levels using a Cox proportional hazards model, it has been shown that high

35

expression of sFRP4 correlates with a poor outcome in patients (n=127) with serous ovarian cancer ($p=0.0056$) (Figure 4B).

EXAMPLE 4

5 *Validation of gene expression profiling results using quantitative RT-PCR*

Candidate diagnostic genes are screened by quantitative RT-PCR against ovarian cancer cell lines to both validate the transcript profiling data (ie check their up- or down-regulation). Candidate diagnostic genes are screened using mRNA isolated from a panel of 9 ovarian tumour cell lines, (A2780, SKOV3, OVCAR-3, IGROV-1, CAOVS, OV-90, 10 SW626, TOV-21G and TOV-112D), in addition to several other tumour cell lines including lines derived from breast, prostate and colorectal tumours, and immortalised (non-transformed) human ovarian surface epithelial cells and a primary normal breast epithelial cell line (184).

15 Total RNA is isolated from the normal and tumour cell lines, reverse transcribed into cDNA and used as template in a quantitative PCR using a LightCycler system (Roche Diagnostics). The relative amount of each gene product is determined by comparison to a standard housekeeping gene (GAPDH).

20 EXAMPLE 5

Identification of Novel Genes for Diagnosis of Ovarian Cancer

We identified candidate genes with diagnostic potential from our list of aberrantly regulated genes by applying the following selection procedure: genes with a good transcript profile and low p-value (ie highly significantly up- or down-regulated in ovarian 25 cancer, as determined in Example 1); and mapping to areas of the genome that have been shown to be amplified or lost in ovarian cancer. Accordingly, it is likely that these genes are involved in the development and progression of ovarian cancer (ie putative oncogenes and tumour suppressor genes). Additional parameters for analysis included known or putative function in oncogenesis (eg signal transduction, regulation of cellular proliferation, apoptosis etc); and association with other forms of other tumours. Genes 30 identified in this analysis are shown in Table 3.

One method for the diagnosis of cancer comprises detecting modified DNA shed by the developing tumour into the blood stream. This can include the detection of mutations in 35 both oncogenes and tumour suppressor genes involved in the development and progression of ovarian cancer. Furthermore, it has been recently shown that aberrant

methylation of tumour suppressor genes, specifically hypermethylation of their gene promoters, frequently accompanies gene silencing in cancers, and indeed in some cases appears to be the predominant mechanism of gene silencing.

- 5 Combined with the knowledge of tumour nucleic acids circulating in the blood that reflect the biological characteristics of a tumour, the detection of methylation-specific tumour suppressor gene signatures for any given tumour type has promise as a specific and sensitive molecular test for detecting and monitoring cancer. Aberrant methylation is a frequent epigenetic event in epithelial ovarian cancer and many candidate tumour
- 10 suppressor genes of epithelial ovarian cancer have been shown to be hypermethylated in epithelial ovarian cancer, such as, for example BRCA1.

- In particular, expression of the candidate tumor suppressor gene MCC, has been shown to be down-regulated in epithelial ovarian cancer compared to normal ovarian tissue.
- 15 MCC appears to be involved in critical cell growth regulatory processes and maps to a chromosomal region hypothesised as containing a tumor suppressor gene in ovarian cancer. Furthermore, we have identified a CpG island within the predicted promoter sequence of the MCC gene, a critical feature of genes that are subject to gene silencing by hypermethylation and a known characteristic of tumor suppressor genes. Taken
- 20 together these data strongly implicate MCC as a candidate tumor suppressor gene involved in epithelial ovarian cancer.

Table 1
Genes having modified expression in subjects suffering from ovarian cancer

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
a. upregulated genes NM_002354	Hs.692:235	Ep-CAM; TACSTD1, tumor-associated calcium signal transducer 1; epithelial glycoprotein	Lymphocyte antigen, plasma membrane, tumor antigen. Member of the GA733 family. C-archoma-associated antigen expressed on most normal epithelial cells and gastrointestinal carcinomas and functions as a homotypic calcium-independent cell adhesion molecule. The antigen is being used as a target for immunotherapy treatment of human carcinomas.	0
	BC008428	Hs.15093:210; Hs.290304:1	HSPC195, hypothetical protein HSPC195	0
	NM_017697	Hs.24743:94	FLJ20171, hypothetical protein FLJ20171	0
AW419198	Hs.257924:13	FLJ13782, Hypothetical protein FLJ13782	contains 3 RNA recognition motifs	0
AW630088	Hs.76550:164	MAL2	weakly similar to a drosophila transcription factor	0
NM_004360	Hs.194657:233	CDH1, cadherin 1, type 1, E-cadherin (epithelial)	Mal2 T-cell differentiation protein; found thru interaction with TPD52 which is overexpressed in breast cancer; 4 TM are involved in vesicle transport	0
NM_003761	Hs.172694:89	VAMP8, vesicle-associated membrane protein 8 (endobrevin)	Tumor suppressor. Ca2+-dependent glycoprotein, mediates cell-cell interactions in epithelial cells. Mutations correlated with gastric, breast, colorectal, thyroid and ovarian cancer. Loss of function thought to contribute to progression in cancer by increasing proliferation, invasion, and/or metastasis. The ectodomain of this protein mediates bacterial adhesion to mammalian cells and the cytoplasmic domain is required for internalization.	0
NM_004415	Hs.349499	DSP, desmoplakin (DPI, DPII)	Early endosome, membrane fraction, non-selective vesicle docking, non-selective vesicle transport, protein complex assembly, synaptic vesicle. Member of a family involved in docking or fusion of synaptic vesicles. Associated with the perinuclear vesicular structures of the early endocytic compartment.	0
NM_013230	Hs.286124:357; Hs.375108	CD24: CD24 antigen (small cell lung carcinoma cluster 4 antigen)	Cell shape and cell size control, cell-cell adherens junction, epidermal differentiation, intermediate filament, structural constituent of cytoskeleton. Acts as a site of attachment for intermediate filaments in desmosomes (intercellular junction in vertebrate epithelial cells). Compound heterozygosity for non-sense and mis-sense mutations underlies skin fragility/woolly hair syndrome. Plasma membrane, humoral defense mechanism. Cell surface antigen; glycosyl phosphatidylinositol (GPI)-linked glycoprotein that differentiates and activates granulocytes and B lymphocytes.	0

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
NM_003710	Hs.233950:84,Hs.182265:2,Hs.7771:1	SPINT1, serine protease inhibitor, Kunitz type 1. Hepatocyte growth factor activator inhibitor.	Extracellular, membrane fraction, serine protease inhibitor. Member of the Kunitz family of serine protease inhibitors. Hepatocyte growth factor activator inhibitor is a potent inhibitor specific for HGF activator and is thought to be involved in regulation of proteolytic activation of HGF in injured tissues.	0
NM_153345	Hs.17558:16	FLJ90586, hypothetical protein	Function unknown	0.0001
NM_015238	Hs.21543:36	KIAA0869, KIAA0869 protein; KIBRA	Function unknown	0.0002
AI282759	Hs.242463:1	KRT8, keratin 8	Cell structure, Cytoskeletal. May form intermediate filaments; type II keratin, member of a family of structural proteins. Disruption of mechanisms that normally regulate keratin expression in vivo could be related to inflammatory and neoplastic pancreatic disorders (Casanova 1999).	0.0002
AI393742	Hs.199067:46	ERBB3, v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	Transmembrane receptor protein tyrosine kinase, epidermal growth factor receptor, integral plasma membrane protein, protein amino acid phosphorylation. Member of the ERBB gene family of receptor tyrosine kinases, elevated levels in certain human mammary tumor cell lines. A receptor for heregulin, capable of mediating HGL-stimulated tyrosine phosphorylation of itself. Epidermal growth factor contains both positive and negative determinants for interaction with. ErbB-2/ErbB-3 heterodimers (Stortelers 2002)	0.0002
AW957300	Hs.294142:167	ESTs, Weakly similar to CYL1_HUMAN CYLICIN I [H.sapiens]	Function unknown	0.0002
NM_012474; W70171	Hs.75939:33,Hs.170864:1	UMPK, uridine monophosphate kinase	Catalyzes the phosphorylation of uridine monophosphate to uridine diphosphate. First step in production of pyrimidine nucleoside triphosphates required for RNA and DNA synthesis. An allele of this gene may play a role in mediating nonhumoral immunity to Hemophilus influenzae type B.	0.0003
AA165082	Hs.146388:47,Hs.113919:3	MAP7, microtubule-associated protein 7	Establishment and/or maintenance of cell polarity, microtubule associated protein, microtubule cytoskeleton organization and biogenesis, structural molecule. Predominantly expressed in cells of epithelial origin. Involved in microtubule dynamics and cell polarization and differentiation. Stabilizes microtubules, and may modulate microtubule functions. Studies of the related mouse protein suggest an essential role in microtubule function required for spermatogenesis.	0.0004
AA284679	Hs.25640:264,Hs.5372:2	CLDN3, claudin 3	Integral plasma membrane protein, pathogenesis, tight junction, transmembrane receptor. Member of the claudin family of integral membrane proteins; receptor for Clostridium perfringens enterotoxin;	0.0004

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
NM_004433	Hs.166098:170	ELF3, E74-like factor 3 (ets domain transcription factor, epithelial-specific)	Embryogenesis and morphogenesis, transcription co-activator, transcription factor, transcription from Pol II promoter. ETS domain transcriptional activator; activates expression of epithelial cell specific genes.	0.0004
AW247252	Hs.75514:181	NP, nucleoside phosphorylase	DNA modification, nucleobase nucleoside nucleotide and nucleic acid metabolism, purine-nucleoside phosphorylase. Enzyme purine nucleoside phosphorylase together with adenosine deaminase (ADA) serves a key role in purine catabolism, referred to as the salvage pathway. Mutations in either enzyme result in a severe combined immunodeficiency (SCID).	0.0004
NM_015925	Hs.361379, Hs.95697:59,Hs.9384 8:1	LISCH7, Liver-specific bHLH-Zip transcription factor	LISCH protein	0.0004
NM_022454	Hs.97884:22	SOX17, SRY (sex determining region Y)-box 17	Likely ortholog of mouse SRY-box containing gene 17; alias SOX17	0.0005
AI124758	Hs.5337:181	IDH2, isocitrate dehydrogenase 2 (NADP+), mitochondrial	Carbohydrate metabolism, mitochondrion	0.0006
NM_003084	Hs.313:273,Hs.29789 5:1	SPP1, secreted phosphoprotein 1 (osteopontin, bone sialoprotein 1, early T-lymphocyte activation 1)	Osteopontin (bone sialoprotein); bone and blood vessel extracellular matrix protein involved in calcification and atherosclerosis. Increased expression is associated with breast tumor metastasis (Urquidí 2002). Role in HCC, especially in cancer-stromal interactions (Golob 2002). Association between levels of a biomarker, osteopontin, and ovarian cancer suggest its clinical usefulness (Kim 2002).	0.0006
BE382756	Hs.169902:319,Hs.27 5406:1	SLC2A1, Solute carrier family 2 (facilitated glucose transporter), member 1	Glucose transporter, membrane fraction. SLC2A1/GLUT1 - facilitated glucose transporter. Glucose transporter is an integral membrane glycoprotein that is involved in transporting glucose into most cells. 12 TMs. Role in transport of glucose across the blood-brain barrier. Consistent marker of ovarian epithelial malignancy (Kair 2002). Marker for discriminating hepatocellular carcinoma from other carcinomas (Zimmernan 2002).	0.0006
BE512730	Hs.65114:718,Hs.279 437:1	KRT18, keratin 18	Cell shape and cell size control, embryogenesis and morphogenesis, intermediate filament, structural constituent of cytoskeleton. Component of intermediate filaments; type I epidermal keratin, strongly similar to murine Endo B. Expressed in single layer epithelial tissues of the body. Mutations linked to cryptogenic cirrhosis.	0.0006

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
NM_001769	Hs.1244:227,Hs.2305 59:1,Hs.242020:1	CD8: CD9 antigen (p24)	Plasma membrane, integral plasma membrane protein. Member of the transmembrane 4 superfamily (TM4SF); may mediate platelet activation and aggregation. Cell surface glycoprotein that is known to complex with integrins and other transmembrane 4 superfamily proteins.	0.0006
A1791905; NM_018027	Hs.95549:147,Hs.229 556:1	FLJ20273, RNA-binding protein	Contains four RNA recognition motifs (RRM, RBD, or RNP)	0.0007
NM_006103	Hs.2718:108,Hs.5445 1:1	WFDC2, WAP four-disulfide core domain 2	Endopeptidase inhibitor, extracellular space, proteolysis and peptidolysis, spermatogenesis. Epididymis-specific secreted protein; may have a role in sperm maturation; arelong to a family of extracellular proteinase inhibitors. Expressed in pulmonary epithelial cells, and also expressed in some ovarian cancers.	0.0008
U81961	Hs.438580	SCNN1A, sodium channel, nonvoltage-gated 1 alpha	Amloride-sensitive sodium channel, excretion, integral plasma membrane protein, membrane fraction, sodium transport. Alpha subunit of the amiloride-sensitive epithelial sodium channel; functions in nonvoltage-gated channel	0.0009
X69699; NM_013952	Hs.73149:72,Hs.2130 08:1	PAX8, paired box gene 8	Histogenesis and organogenesis, embryogenesis and morphogenesis, thyroid-stimulating hormone receptor, transcription factor. Member of the paired domain family of nuclear transcription factors; are involved in the ribosome assembly, required for normal thyroid development. PAX genes play critical roles during fetal development and cancer growth.	0.0009
A1027643	Hs.120912:12	EST's	Function unknown	0.001
AA173892	Hs.7956:28	EST's	Function unknown	0.0011
AB018249	Hs.10458:10	SCYA16, small inducible cytokine subfamily A (Cys-Cys), member 16.	Antimicrobial humoral response (sensu Invertebrata), cell-cell signalling, chemokine chemotaxis. Cytokine A16; lymphocyte and monocyte chemoattractant.	0.0011
NM_014791	Hs.184339:27	MELK, likely ortholog of maternal embryonic leucine zipper kinase.	KIAA0175 gene product; serine/threonine protein kinase domain	0.0011
NM_030674	Hs.18272:81	SLC38A1, solute carrier family 38, member 1	amino acid transporter A1 (ATA1), likely ortholog of mouse N-system amino acid transporter protein NAT2.	0.0012
NM_005882	Hs.6527:201	GPR56, G protein-coupled receptor 56	cell adhesion, cell-cell signalling, G-protein linked receptor, integral plasma membrane protein, G-protein linked receptor protein signalling pathway. Member of the G protein-coupled receptor family; similar to secretin and calcitonin receptors. 7 transmembrane domains, a much-like domain and cysteine box in the N-terminal region. Expressed in range of tissues, highest levels in thyroid, selectively within the monolayer of cuboidal epithelial cells of the smaller, more actively secreting follicles of human thyroid. Differentially expressed in melanoma cell lines with different	0.0012

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
A1669760	Hs.188881:6,Hs.199354:1	ESTs	metastatic potential (Zandman et al 1999).	0.0013
NM_001730	Hs.84728:127	KLF5, Kruppel-like factor 5 (intestinal)	dbEST Library Tissue Type restricted to prostate	0.0014
A1355761	Hs.242463:2	KRT8, keratin 8	RNA polymerase II transcription factor, transcription from Pol II promoter. Zinc finger transcriptional activator; localizes to the nucleus and binds the epidermal growth factor response element, binds GC boxes. Cell structure, Cytoskeletal. May form intermediate filaments; type II keratin, member of a family of structural proteins. Disruption of mechanisms that normally regulate keratin expression in vivo could be related to inflammatory and neoplastic pancreatic disorders (Casanova 1999).	0.0014
BE019020	Hs.85838:171	SLC18A3, solute carrier family 16 (monocarboxylic acid transporters), member 3 (MCT3)	Integral plasma membrane protein, membrane fraction, monocarboxylic acid transport, monocarboxylic acid transporter. Member of monocarboxylate transporter family, may function as a transporter (MCT3).	0.0015
NM_001307 NM_002266	Hs.278562:101 Hs.159557:394	CLDN7, claudin 7 KPNA2, karyopherin alpha 2 (RAG cohort 1, Importin alpha 1)	Integral membrane protein, tight junction. Similar to murine Cldn7; DNA metabolism, G2 phase of mitotic cell cycle. NLS-bearing substrate-nucleus import, cytoplasm, importin alpha-subunit, nuclear localization sequence binding, nucleoplasm, regulation of DNA recombination, spindle pole body and microtubule cycle (sensu Saccharomyces). Karyopherin alpha 2 (Importin alpha 1); subunit of the NLS (nuclear localization signal) receptor. KPNA2 protein interacts with the NLSs of DNA helicase Q1 and SV40 T antigen and are involved in the nuclear transport of proteins. KPNA2 also may play a role in V(D)J recombination. function unknown	0.0016 0.0016
AW176120	Hs.9061:77	MGC2477, hypothetical protein MGC2477		0.0016
BE265489	Hs.3123:49	LLGL2, lethal giant larvae (Drosophila) homolog 2	Cytoskeleton, structural molecule. May associate with nonmuscle myosin II heavy chain. cDNA source cancer cell lines. 57% ID to m.musculus 1820382A tumor suppressor gene mgl1	0.0016
BE279383	Hs.28557:77	PKP3, plakophilin 3	Cell adhesion, intercellular junction. Desmosomal plaque proteins are members of the 'armadillo-repeat' multigene family and have important functions in cytoskeleton/cell membrane interactions.	0.0018

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
J05581; NM_002456	Hs.89603:128;Hs.296789:1	MUC1, mucin 1, transmembrane	Integral plasma membrane protein. Cell surface mucin glycoprotein expressed by most glandular and ductal epithelial cells and some hematopoietic cell lineages. Alterations in glycosylation in epithelial cancer cells. Marker for hepatocellular carcinoma. MUC1 metabolic complex conserved in tumor-derived and normal epithelial cells. Expression predictor of surgical outcome in mass-forming intrahepatic cholangiocarcinoma. Tyrosine kinase c-Src constitutes a bridge between cystic fibrosis transmembrane regulator channel failure and MUC1 overexpression in cystic fibrosis.	0.0016
AA531276	Hs.59509:9	ESTs (unnamed protein product)	Function unknown	0.0017
AW167128	Hs.231834:3	ESTs; weakly similar to A57717 transcription factor EC2	Function unknown	0.0018
AW368226	Hs.67928:25;Hs.229840:1	Ets-related transcription factor, ESX, epithelium-restricted Ets protein ESX-not in Unigene, but found using resourcer.	Embryogenesis and morphogenesis, transcription co-activator, transcription factor, transcription from Pol II promoter.	0.0021
AK000733	Hs.23900:82	RACGAP1, Rac GTPase activating protein 1	Strongly similar to murine Racgap1 GTPase-activating protein for rac. The plexin-B1/Rac interaction inhibits PAK activation and enhances Semaphorin 4D ligand binding	0.0024
NM_014736	Hs.81892:95	KIAA0101 gene product	function unknown; no significant hits with Superfamily	0.0025
NM_014586	Hs.109437:17	HUNK, hormonally upregulated neu tumor-associated kinase	Developmental processes, protein serine/threonine kinase, signal transduction, protein kinase containing SNF1 (fam of serine/threonine kinases) domain; progesterone and estradiol regulated. Similar to murine Hunk.	0.0025
A1885516	Hs.96612:31;Hs.251688:1	desmocollin type 2a, desmocollin 2, isoform Dsc2b preproprotein; desmosomal glycoprotein II/III; desmocollin-3-not in Unigene, but found using resourcer.	Cell adhesion, intercellular junction	0.0027
AW194426	Hs.20726:17	ESTs	Function unknown	0.0027
NM_001982	Hs.198067:83;Hs.167386:1	ERBB3, HER3 (c-erb-B3), v-erb-b2 erythroblastic leukemia viral oncogene homolog 3 (avian)	Epidermal growth factor receptor, integral plasma membrane protein, protein amino acid phosphorylation. Member of the ERBB gene family of receptor tyrosine kinases, elevated levels in certain human mammary tumor cell lines. A receptor for heregulin, capable of mediating HGF-stimulated tyrosine phosphorylation of itself.	0.0028
NM_007019	Hs.93002:85	UBE2C, ubiquitin carrier protein E2-C	Ubiquitin-dependent protein degradation, degradation of cyclin, protein modification, positive control of cell proliferation. Subunit of a complex with ubiquitin ligase activity; complex that exhibits cyclin-selective ubiquitin ligase activity.	0.0031

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
BE184455	Hs.251754:128,Hs.245742:1	SLPI, secretory leukocyte protease inhibitor (antileukoprotease)	Plasma protein, proteinase inhibitor. Secreted inhibitor which protects epithelial tissues from serine proteases. Found in various secretions including seminal plasma, cervical mucus, and bronchial secretions, has affinity for trypsin, leukocyte elastase, and cathepsin G. Its inhibitory effect contributes to the immune response by protecting epithelial surfaces from attack by endogenous proteolytic enzymes; the protein is also thought to have broad-spectrum anti-biotic activity.	0.0034
Y00815; NM_002840	Hs.75216:262,Hs.228792:1,Hs.245063:1	PTPRF, protein tyrosine phosphatase, receptor type, F	Cell adhesion, integral plasma membrane protein, transmembrane receptor protein, tyrosine phosphatase signaling pathway. Receptor-type protein tyrosine phosphatase F: Interacts with the Insulin receptor; has Ig-like and FN-III repeats in the extracellular domain	0.0035
AA706017	Hs.119944:14	ESTs	Function unknown	0.0038
AA256641	Hs.236894:24	ESTs, Highly similar to S02392 alpha-2-macroglobulin receptor precursor	Function unknown	0.0041
AW055308	Hs.31803:15	ESTs, Weakly similar to TRHY_HUMAN TRICHOHYALI [H.sapiens]	Function unknown	0.0043
AI301558	Hs.290801:35, Hs.356228	EST	Function unknown	0.0044
T18997	Hs.180372:119; Hs.394609	BCL2-like 1, Homo sapiens cDNA FLJ20750 fis, clone HEP05174 (hypothetical protein)	Function unknown	0.0044
AI798863	Hs.87191:8	ESTs	Function unknown	0.0049
JO3258	Hs.2062:146	VDR, vitamin D (1,25-dihydroxyvitamin D3) receptor	DNA binding, signal transduction, vitamin D3 receptor. Zinc-finger DNA-binding transcription factor. Genetic polymorphism determines bone mineral density. Stat1-vitamin D receptor interactions antagonize 1,25-dihydroxyvitamin D transcriptional activity and enhance stat1-mediated transcription.	0.0049
AA151647	Hs.68877:141,Hs.228686:1	CYBA, cytochrome b-245, alpha polypeptide	Cytochrome b, membrane, mitochondrion, superoxide metabolism. Alpha-subunit of cytochrome b245, primary component of the microbicidal oxidase system of phagocytes. CYBA deficiency is associated with chronic granulomatous disease (CGD).	0.005

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AI538613	Hs.135657:8	TMPRSS3 Transmembrane protease, serine 3	Integral membrane protein, proteolysis and peptidolysis. Contains a serine protease domain, a transmembrane domain, a LDL receptor-like domain, and a scavenger receptor cysteine-rich domain. Serine proteases are known to be involved in a variety of biological processes, whose malfunction often leads to human diseases and disorders. Expressed in fetal cochlea and many other tissues, and is thought to be involved in the development and maintenance of the inner ear or the contents of the perilymph and endolymph. Missense mutations in autosomal recessive sensorineural deafness. Identified as a tumor associated gene that is overexpressed in ovarian tumors. Function unknown	0.0051
NM_018000	Hs.79741:18	FLJ10116, hypothetical protein FLJ10116		0.0051
NM_144724	Hs.124740:18	hypothetical protein FLJ30532	59% identity to human Zinc finger protein 91	0.0051
AJ278016	Hs.55565:35	ANKRD3, ankyrin repeat domain 3	ATP binding, protein amino acid phosphorylation, protein binding, protein serine/threonine kinase.	0.0055
NM_013994	Hs.75562:147	DDR1, discoidin domain receptor family, member 1	Cell adhesion, integral plasma membrane protein, transmembrane receptor, protein tyrosine kinase. Epithelial-specific receptor protein tyrosine kinase; are involved in cell adhesion; has putative discoidin motifs in extracellular domain. DDR1 (CD167a) is a RTK that is widely expressed in normal and transformed epithelial cells and is activated by various types of collagen.	0.0055
T09997: NM_001312	Hs.70327:196,Hs.211478:1	CRIP-2, cysteine-rich protein 2	Zn-finger LIM domain protein;208-amino acid protein containing 2 LIM domains	0.0055
BE302796	Hs.105097:115	TK1, thymidine kinase 1, soluble	Cytoplasm, thymidine kinase. Generates thymidylate for DNA synthesis. TK1 gene expression together with TS, TP and DPD gene expression may play important roles in influencing the malignant behavior of epithelial ovarian cancer (Fujiwaki R 2002).	0.006
NM_001067	Hs.156346:184,Hs.270810:2	TOP2A, topoisomerase (DNA) II alpha (170kD)	DNA binding, DNA topoisomerase (ATP-hydrolyzing), nucleus. DNA topoisomerase II alpha; may relax DNA torsion upon replication or transcription. Involved in processes such as chromosome condensation, chromatid separation, and the relief of torsional stress that occurs during DNA transcription and replication. Catalyzes the transient breaking and rejoining of two strands of duplex DNA. The gene encoding this enzyme functions as the target for several anticancer agents and a variety of mutations in this gene have been associated with the development of drug resistance. Reduced activity of this enzyme may also play a role in ataxia-telangiectasia.	0.006

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
U46455	Hs.252189:148,Hs.248217:1	SDC4, syndecan 4 (amphiglycan, ryudocan)	Integral plasma membrane, proteoglycan syndecan. Syndecans are transmembrane heparan sulfate proteoglycans that appear to act as receptors or coreceptors involved in intracellular communication. Members of the MYC gene family and 4 members of the syndecan gene family are closely situated on 4 different chromosomes.	0.0061
M79141	Hs.13234:39	ESTs	Function unknown	0.0062
A1955040	Hs.301584:5,Hs.265398:3	ESTs, Moderately similar to hypothetical protein FLJ20378 [Homo sapiens]	Function unknown	0.0085
NM_005560	Hs.11669:81,Hs.231010:1	LAMA5, laminin, alpha 5	Basement lamina, structural molecule. Widely expressed in adult tissues, with highest levels in lung, heart, and kidney. Fifth member of the alpha subfamily of vertebrate laminin chains. Possible basement membrane protein; contains laminin EGF-like domain, two extracellular laminin G domains.	0.0066
BE563085	Hs.833:97	ISG15, interferon-stimulated protein, 15 kDa	Cell-cell signaling, cytoplasm, extracellular space, protein binding. Protein that is induced by interferon.	0.0068
BE278288	Hs.155048:119	LU, Lutheran blood group (Auberg b antigen included)	Blood group antigen, cell adhesion, integral plasma membrane protein, signal transduction, transmembrane receptor. Lutheran blood group glycoprotein; may play role in cell-cell, cell-matrix adhesion, signal transduction; member of the Ig superfamily, has integrin-binding motifs, SH3 domains.	0.0069
NM_020859	Hs.278628:52	ShrmL, Shroom-related protein (KIAA1481 protein)	Amiloride-sensitive sodium channel (weakly similar to Mus musculus PDZ domain actin binding protein)	0.0074
A1282789	Hs.93859:52	ERP70, protein disulfide isomerase related protein (calcium-binding protein, intestinal-related)	Endoplasmic reticulum lumen, protein secretion. Strongly similar to rat Rn.4070 (CABP2); may bind caldium.	0.008
NM_006147	Hs.11801:77	IRF6, interferon regulatory factor 6	Member 6 of the interferon regulatory factor transcription factor family; has low similarity to IRF4, which is a lymphocytic transcription factor that stimulates B cell proliferation.	0.0082
R61463	Hs.16165:50	LAK-4P, expressed in activated TILAK lymphocytes	expressed in activated TILAK lymphocytes	0.0082
A1878857: NM_016185	Hs.109706:285	HN1, hematological and neurological expressed 1 protein	Strongly similar to murine Hn1	0.0087
AK001763	Hs.73239:37	FLJ10901, hypothetical protein FLJ10901	B link shows some homology to KIAA1294 but no known function	0.009

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AC004770	Hs.4756:99	FEN1, flap structure-specific endonuclease 1	DNA repair enzyme, DNA replication, UV protection, double-strand break repair, double-stranded DNA binding, double-stranded DNA specific exodeoxyribonuclease, endonuclease, fatty acid desaturation, membrane fraction. Removes 5' overhanging flaps in DNA repair and processes the 5' ends of Okazaki fragments in lagging strand DNA synthesis.	0.0093
AI567421	Hs.273330:137	AGRN: agrin	Aggrin is a neuronal aggregating factor that induces the aggregation of acetylcholine receptors and other postsynaptic proteins on muscle fibers and is crucial for the formation of the neuromuscular junction. Acts at the nerve-muscle synapse in the glomerular basal membrane and on T-lymphocytes.	0.0093
AW161386	Hs.13561:49	MGC4692: hypothetical protein MGC4692	Function unknown	0.0103
M85430	Hs.155191:546	VIL2, villin 2 (ezrin)	Cytoskeletal anchoring, microvillus. Regulates cell adhesion and cortical morphogenesis. The cytoplasmic peripheral membrane protein encoded by this gene functions as a protein-tyrosine kinase substrate in microvilli. As a member of the ERM protein family, this protein serves as an intermediate between the plasma membrane and the actin cytoskeleton. It plays a key role in cell surface structure adhesion, migration, and organization.	0.0108
AW250380	Hs.108059:124,Hs.24756:11	MRPL12, mitochondrial ribosomal protein L12	Protein synthesis, General cellular role. Ribosomal subunit, Mitochondrial, RNA-binding protein, Ribosome-associated.	0.0114
AI733848; NM_021220	Hs.71935:13	ZNF339, zinc finger protein 339	Zinc finger protein	0.0115
AF111856; NM_006424	Hs.105039:48	SLC34A2, solute carrier family 34 (sodium phosphate), member 2	SLC34A2: solute carrier family 34 (sodium phosphate), member 2; contains 8 predicted TMs and a cysteine-rich N-terminal region. Type 2 sodium-dependent phosphate transporter. member of the renal type II co-transporter family.	0.0121
BE386983; NM_138410	Hs.343214	CKLFSF7: chemokine-like factor super family 7	chemokine-like factor gene superfamily; transmb 4 superfamily	0.0131
AA433988	Hs.98502:8	MUC16, mucin 16, CA125	Mucin 16. Alias CA125 ovarian cancer antigen	0.0137
AW248314	Hs.9822:83	MRPS18A, mitochondrial ribosomal protein S18A	Mitochondrial small ribosomal subunit, protein biosynthesis, structural constituent of ribosome/ribosomal mitochondrial protein S18A	0.0149

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AA454501	Hs.43866:65	PTP4A3, protein tyrosine phosphatase type IVA, member 3	Phenylated protein tyrosine phosphatase. PTPs are cell signaling molecules that play regulatory roles in a variety of cellular processes. Strong similarity to murine Ptp4a3 (Mm.4124). Overexpression of this gene in mammalian cells was reported to inhibit angiotensin-II induced cell calcium mobilization and promote cell growth. PRL3 (PTP4A3) expressed at high levels cancer metastases (Saha et al. 2001). PRL3 gene is important for colorectal cancer metastasis.	0.016
U33446	Hs.75799:116	PRSS8, protease, serine, 8 (prostasin)	Extracellular space, plasma membrane, serine type peptidase. A trypsinogen, member of the trypsin family of serine proteases. Highly expressed in prostate epithelia, one of several proteolytic enzymes found in seminal fluid. Protease-mediated regulation of sodium absorption is a function of human airway epithelia, and prostasin is a likely candidate for this activity.	0.0166
X98654	Hs.93837:43	PITPNM, phosphatidylinositol transfer protein, membrane-associated	Brain development, lipid metabolism, membrane fraction, phosphatidylinositol transporter, phototransduction. Catalyzes the transfer of phosphatidylinositol between membranes; similar to <i>Drosophila</i> rdgB.	0.0167
AI660149	Hs.44865:39, Hs.3008 19:19, Hs.293904:14	LEF1, Lymphoid enhancer-binding factor-1	Very strongly similar to murine Lef1, may act as a transcription factor. Expressed in pre-B and T cells. Binds to T-cell receptor-alpha enhancer and confers maximal enhancer activity. A target gene ectopically activated in colon cancer, from selective activation of a promoter for a full-length LEF1 isoform that binds beta-catenin (HOVANES 2001).	0.0172
AF098158; NM_012112	Hs.9329:152	C20orf1, chromosome 20 open reading frame 1	ATP binding, GTP binding, cell proliferation, mitosis, nucleus spindle. Proliferation-associated nuclear protein; associates with the spindle pole and mitotic spindle during mitosis	0.0183
AB014551	Hs.155120:101, Hs.337774	ARHGEF2, rho/rac guanine nucleotide exchange factor (GEF) 2	Cell shape and cell size control, cell surface receptor linked signal transduction, guanylnucleotide exchange factor, microtubule cytoskeleton. Rho GTPases play a fundamental role in numerous cellular processes that are initiated by extracellular stimuli that work through G protein coupled receptors. The encoded protein may form complex with G proteins and stimulate Rho-dependent signals. Rho/Rac guanine nucleotide exchange factor (GEF) 2; associates with microtubules, stimulates GTP binding on Rac and Rho	0.0206
AI278023	Hs.89866:24, Hs.2907 80:1	ESTs	Function unknown	0.0208

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
Z95152	Hs.178695:25,Hs.79107:1	MAPK13, mitogen-activated protein kinase 13	MAP kinase, antimicrobial humoral response (sensu Invertebrata), cell surface receptor, signal transduction, chemotaxis, stress response. MAP kinases act as an integration point for multiple biochemical signals, and are involved in a wide variety of cellular processes such as proliferation, differentiation, transcription regulation and development. Are activated by proinflammatory cytokines and cellular stress. Transcription factor ATF2, and microtubule dynamics regulator stathmin are substrates of this kinase.	0.0217
AW840171	Hs.265398:7	ESTs. Moderately similar to hypothetical protein FLJ20378 [Homo sapiens] [H.sapiens]	Function unknown	0.0222
D49441	Hs.155981:53	MSLN, mesothelin	Cell adhesion, cell surface antigen, membrane. Pre-pro-megakaryocyte potentiating factor. An antibody that reacts with ovarian cancers and mesotheliomas was used to isolate a cell surface antigen named mesothelin. Although the function of mesothelin is unknown, it may play a role in cellular adhesion and is present on mesothelium, mesotheliomas, and ovarian cancers.	0.0225
AW797437	Hs.69771:282,Hs.444:1,Hs.294163:1	EST, CM1-UM0039-030400-173-a09	Function unknown	0.0229
BE396290	Hs.5097:261	SYNGR2, synaptogyrin 2	Integral plasma membrane protein, member of a family of transmembrane synaptic vesicle proteins, specialized secretory organelles that store neurotransmitters in nerve terminals, and release them by fusing with the presynaptic plasma membrane during exocytosis.	0.0229
AI656166; NM_025080	Hs.7331	ASRGL1; asparaginase like 1	glycoprotein catabolism	0.02
NM_002145	Hs.2733:25	HOXB2, homeo box B2, Hox2H protein	Circulation, developmental processes, transcription factor. Member of homeodomain family of DNA binding proteins; may regulate gene expression, morphogenesis, and differentiation. Genes of the HOXB (or HOX2) complex are expressed specifically in erythromegakaryocytic cell lines, some are expressed only in hematopoietic progenitors.	0.024
AW959311	Hs.87018:8; Hs.172012	Hypothetical protein DKFZp434J037	probable serine/threonine protein kinase; KIAA0537	0.0251

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
NM_000269	Hs.118638:186,Hs.276104:1,Hs.276127:1,Hs.276246:1	NME1, non-metastatic cells 1, protein (NM23A)	Transcription factor and nucleoside diphosphate kinase; has a role in the transcriptional regulation of c-myc expression. Mutations in NME1 have been identified in aggressive neuroblastomas.	0.0257
AA379597	Hs.5188:87,Hs.277192:1	HSPC150, HSPC150 protein similar to ubiquitin-conjugating enzyme	Similar to ubiquitin conjugating enzyme	0.0259
BE148235	Hs.193063:100	Homo sapiens cDNA FLJ14201 fis, clone NT2RP3002955	high homology to ARP-3 actin-like protein	0.0259
AI683243; AI587638	Hs.97258	ESTs	Mod similarly to S29539 ribosomal protein L13a	0.03
AF111713	Hs.286218:64	JAM1, junctional adhesion molecule	Cell motility, inflammatory response, intercellular junction. Role in the regulation of tight junction assembly in epithelia. Ligand of JAM is required for reovirus-induced activation of NF-kappa-B and apoptosis. Role in lymphocyte homing.	0.0261
BE391635	Hs.75725:450,Hs.274751:1,Hs.277482:1,Hs.277468:1	TAGLN2, transgelin 2	Complex assembly protein. Homolog of the protein transgelin, which is one of the earliest markers of differentiated smooth muscle. Function not yet determined. Are an actin-binding protein.	0.0275
D14697	Hs.77393:201,Hs.247769:1	FOPS, farnesyl diphosphate synthase (farnesyl pyrophosphate synthetase, dimethylallyltransferase, geranyltransferase)	Farnesyl pyrophosphate synthetase (farnesyl diphosphate synthase); part of the cholesterol synthesis pathway.	0.0276
AW194364	Hs.94814	MGC2865, Hypothetical protein MGC2865	Function unknown.	0.0295
T47364	Hs.278613:145	IFI27, interferon, alpha-inducible protein 27	Integral membrane protein. Isolated from estradiol-treated human breast carcinoma cells. Induced by interferon-alpha in human cell lines of different origin, expression is independent of the presence of estradiol receptor in the cells.	0.03
U17760	Hs.301103:71,Hs.75517:24,Hs.199068:1	LAMB3, Laminin, beta 3 (nibelin (125kD), kalinin (140kD), BM600 (125kD)) (Acan NM_000228)	Epidermal differentiation, laminin-5, structural molecule. Member of a family of basement membrane proteins. LAMB3 serves as the beta chain in laminin-5. Mutations in LAMB3 have been identified as the cause of various types of epidermolysis bullosa.	0.0304
AU076517	Hs.184276:142	SLC9A3R1, solute carrier family 9 (sodium/hydrogen exchanger), isoform 3 regulatory factor 1	Actin cytoskeleton, protein complex assembly. Regulatory cofactor of the NHE3 (SLC9A3) sodium/hydrogen antiporter; interacts with merlin (NF2) and ERM family members; has two PDZ domains. Structural determinants in interaction of beta 2 adrenergic and platelet-derived growth factor receptors	0.0312

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AW880841	Hs.96908, Hs.74427:112	PIG11, p53-induced protein	Negative control of cell proliferation, stress response. May generate or respond to oxidative stress, may have a role in p53-dependent apoptosis Polyak K, Xia Y, Zweier JL, Kinzler KW, Vogelstein B. A model for p53-induced apoptosis. Nature. 1997 Sep 18;389(6648):300-5.	0.0314
H24185 BE614410	Hs.92918:91 Hs.23044:51	BM-008, hypothetical protein BM-008 MGC18386, hypothetical protein, similar to RIKEN cDNA	Function unknown.	0.0314 0.0326
H16423	Hs.82685:37	CD47, CD47 antigen (Rh-related antigen, integrin-associated signal transducer)	Oncogenesis, plasma membrane, plasma glycoprotein, cell-cell matrix adhesion, integral plasma membrane proteoglycan, integrin receptor signal signalling pathway. Similar to Rh-antigen; may interact with integrins and have a role in intracellular calcium increase during cell adhesion.	0.0336
AU076611; NM_006636	Hs.154872:123	MTHFD2, methylene tetrahydrofolate dehydrogenase (NADP+ dependent); methenyltetrahydrofolate cyclohydrolase	Electron transporter, methenyltetrahydrofolate cyclohydrolase, mitochondrion. encodes a nuclear-encoded mitochondrial bifunctional enzyme with methenyltetrahydrofolate dehydrogenase and methenyltetrahydrofolate cyclohydrolase activities. may provide formyltetrahydrofolate for formylmethionyl tRNA synthesis; involved in initiation of mitochondrial protein synthesis.	0.0342
AI859390	Hs.288940:49	TMEM8, five-span transmembrane protein M83; type I transmembrane protein	Integral plasma membrane protein. Type I transmembrane protein; contains five membrane-spanning domains	0.0345
AA159216	Hs.55505:57	FLJ20442, hypothetical protein FLJ20442	Contains a dual specificity protein phosphatase catalytic domain; 34% similar to protein-tyrosine phosphatase	0.0354
AF119665; NM_021129	Hs.184011:156	PP, pyrophosphatase (inorganic)	Inorganic diphosphatase, phosphate metabolism. Catalyzes the hydrolysis of pyrophosphate to inorganic phosphate	0.0358
BE513613; NM_005720	Hs.11538:275	ARPC1B, actin related protein 2/3 complex, subunit 1A (41 kD)	Cell motility, structural constituent of cytoskeleton. Arp2/3 complex, subunit 1A; involved in assembly of the actin cytoskeleton, may have a role in protrusion of lamellipodia	0.0367
NM_012153	Hs.182339	EHF; ets homologous factor	DNA binding, tumor suppressor, cell proliferation, developmental processes, transcription activating factor. Member of the ESE subfamily of Ets transcription factors	0.0404
AW772298	Hs.21103:40;Hs.2667 84:2;Hs.102950:1	Homo sapiens mRNA; cDNA DKFZp564B076 (from clone DKFZp564B076)	Alias coat protein gamma-cop	0.0423
H16646	Hs.118666:66	PP591, hypothetical protein PP591	Hypothetical protein PP591 (Novel Human cDNA clones with function of inhibiting cancer cell growth; unpublished)	0.043

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AA279661	Hs.83753:244;Hs.301236:3	SNRPB, small nuclear ribonucleoprotein polypeptides B and B1	Spliceosome, mRNA splicing, small nuclear ribonucleoprotein. U1 and U2 snRNP protein; component of snRNP complexes, required units of the spliceosome	0.0446
BE001596	Hs.85266:102	ITGB4, integrin, beta 4	Cell adhesion receptor, integrin. Invasive growth, oncogenesis. Beta 4 subunit of integrin, involved in cell-cell and cell-matrix interactions; member of a family of cell-surface proteins. Binding of beta 4 to plectin is essential for the proper formation and function of hemidesmosomes.	0.0453
BE246444	Hs.283685:148;Hs.232028:2	FLJ20396, hypothetical protein FLJ20396	100%/175aa unnamed protein g7020468	0.0453
X54942	Hs.83758:34	CKS2, CDC28 protein kinase 2	Cell proliferation, regulation of CDK activity. Similar to S. pombe p13suc1; binds and regulates CDK-cyclin complexes. expressed in different patterns through the cell cycle in HeLa cells, which reflects specialized role for the encoded protein.	0.0478
AA305599	Hs.238205:36	PRO2013, hypothetical protein PRO2013	Function unknown	0.0483
AF019226	Hs.8036:84	RAB3D, member RAS oncogene family	RAB small monomeric GTPase, hemocyte development. GTP-binding protein; are involved in vesicle transport; member of the RAB family of small GTPases. Alias GOV, that is overexpressed in glioblastoma multiforme tissue as compared to normal brain tissue. GOV is also highly expressed in recurrent glioma, colon tumor metastatic to brain, breast tumors, prostate tumors, and several tumor cell lines	0.0485
NM_001949	Hs.1189:65;Hs.296939:2	E2F3, E2F transcription factor 3	Protein binding, transcription factor, transcription initiation from Pol II promoter. Involved in cell cycle regulation, binds retinoblastoma protein (Rb). E2F family plays a crucial role in the control of cell cycle and action of tumor suppressor proteins and is also a target of the transforming proteins of small DNA tumor viruses.	0.049
AF217513	Hs.279905:73;Hs.283849:4	ANKT, nucleolar protein ANKT	clone HQ0310 PRO0310p1 nucleolar protein ANKT - no functional data	0.0504
AW513143	Hs.98367:8	ESTs	Expressed in uterus	0.0535
AJ245671	Hs.12844:73	EGFL6, EGF-like-domain; multiple 6	Cell cycle, oncogenesis, integrin ligand, extracellular space. Member of the epidermal growth factor (EGF) repeat superfamily; contains an EGF-like-domain. Expressed early during development, and its expression has been detected in lung and meningioma tumors.	0.0568
AA084248	Hs.85339:64	GPR39, G protein-coupled receptor 39	G-protein linked receptor, G-protein coupled receptor protein signalling pathway, integral plasma membrane protein.	0.19

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
U62801	Hs.79361:65	KLK6, kallikrein 6 (neurosin, zyme)	Serine type peptidase, pathogenesis. Neurosin (protease M, zyme); a serine protease that cleaves amyloid precursor protein (APP). Growing evidence suggests that many kallikreins are implicated in carcinogenesis and some have potential as novel cancer and other disease biomarkers.	0.0159
D49441	Hs.155981:53	MSLN, mesothelin	Cell adhesion, cell surface antigen, membrane. Pre-pro-megakaryocyte potentiating factor. An antibody that reacts with ovarian cancers and mesotheliomas was used to isolate a cell surface antigen named mesothelin. Although the function of mesothelin is unknown, it may play a role in cellular adhesion and is present on mesothelium, mesotheliomas, and ovarian cancers.	0.147
X51630	Hs.1145:22,Hs.29685 1:1	WT1, Wilms tumor 1	Nucleus, transcription factor, transcription regulation. 4 Zn finger domains. Functions in kidney and gonad proliferation and differentiation. Mutations in this gene are associated with the development of Wilms tumors in the kidney or with abnormalities of the genitourinary tract.	0.2938
AB018305	Hs.5378:149	SPON1, spondin 1, (f-spondin) extracellular matrix protein	Extracellular matrix protein. Very strongly similar to rat F-spondin (Rn.7546); may have a role in the growth and guidance of axons.	0.3394
AA433988	Hs.98502:8	MUC16, mucin 16, CA125	Mucin 16. Alias CA125 ovarian cancer antigen	0.6568
NM_006149	Hs.5302:132	LGALS4, lectin, galactoside-binding, soluble, 4 (galectin 4)	Lectin, cytosol, cell adhesion, plasma membrane. Binds to beta galactoside, involved in cell adhesion, cell growth regulation, inflammation, immunomodulation, apoptosis and metastasis; member of a family of lectins. LGALS4 is an S-type lectin that is strongly underexpressed in colorectal cancer.	0.0001
AA315933	Hs.120879:17	Homo sapiens, clone MGC:32871 IMAGE:4733535, mRNA, complete cds	Function unknown	0.0001
U47732	Hs.84072:110	TM4SF3, transmembrane 4 superfamily member 3	Integral plasma membrane protein, lysosome, pathogenesis, protein amino acid glycosylation, signal transducer, tumor antigen. Cell surface glycoprotein defined by the monoclonal antibody CO-029 is a 27- to 34-kD membrane protein expressed in gastric, colon, rectal, and pancreatic carcinomas but not in most normal tissues	0.0028

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
NM_005588	Hs.179704	MEP1A, meprin A alpha, PABA peptide hydrolase	metalloproteinase located apically and secreted by epithelial cells in normal colon; degrades broad range of ECM components in vitro; proposed role in tumour progression by facilitating migration, intravasation and metastasis	0.01
AW503395	Hs.5541:112	ATP2A3, ATPase, Ca++ transporting, ubiquitous	Endoplasmic reticulum, adenosinetriphosphatase, small molecule transport, calcium-transporting ATPase, integral plasma membrane protein. Sarco/endoplasmic reticulum Ca2+-ATPase; pumps calcium.	0.0154
NM_004063	Hs.89436:50	CDH17, cadherin 17, LI cadherin (liver-intestine)	Cell adhesion, integral plasma membrane protein, membrane fraction, small molecule transport, transporter. Member of the cadherin family of calcium-dependent glycoproteins; facilitates uptake of peptide-based drugs, may mediate cell-cell interactions. Component of the gastrointestinal tract and pancreatic ducts, intestinal proton-dependent peptide transporter in the first step in oral absorption of many medically important peptide-based drugs.	0.0172
A1073913	Hs.100686:20	LOC155465, anterior gradient protein 3	Oncogenesis	0.0266
A1928445	Hs.92254:80	SYTL2: synaptotagmin-like 2	Synaptotagmin-like protein of the C2 domain-containing family of proteins. Although the specific function of the synaptotagmin-like proteins is unknown, a role in regulation of synaptic vesicle trafficking via their C2 domains has been suggested. Region of weak similarity to murine Gph	0.08
W40460	Hs.144442:5	PLA2G10: phospholipase A2, group X	Extracellular, secreted phospholipase A2. Group X secretory phospholipase_a2; hydrolyzes the phospholipid sn-2 ester bond; member of the phospholipase family	0.1888
AA132981	Hs.212533:4	Homo sapiens cDNA: FLJ22572 fs, clone HSI02313	Function unknown	0.1965
AF111856	Hs.105039:48	SLC34A2, solute carrier family 34 (sodium phosphate), member 2	SLC34A2: solute carrier family 34 (sodium phosphate), member 2; contains 8 predicted TMs and a cysteine-rich N-terminal region. Type 2 sodium-dependent phosphate transporter. member of the renal type II co-transporter family.	0.5078
AA143654		zo65a02.r1 Stratagene pancreas (#937208) Homo sapiens cDNA clone IMAGE:591722 5', mRNA sequence	Function unknown	0.036

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
b. prognostic indicators				
AA046217	Hs.105370:2	ESTs	Function unknown	0.00
NM_015902		EDD:Homo sapiens progesterin induced protein (DD5), mRNA, VERSION NM_020987.1 GI	Soluble fraction, cell proliferation, ubiquitin-protein ligase, ubiquitin conjugating enzyme, ubiquitin-dependent protein degradation. Member of the HECT family of proteins; may function as an E3 ubiquitin-protein ligase. This gene is localized to chromosome 8q22, a locus disrupted in a variety of cancers. This gene potentially has a role in regulation of cell proliferation or differentiation.	0.00
T83882	Hs.97927:20	ESTs	Function unknown	0.01
#(NOCAT)		NM_001615:Homo sapiens actin, gamma 2, smooth muscle, enteric (ACTG2), mRNA, variant 1, mRNA.	Structural protein of muscle. Gamma 2 actin; enteric-type, smooth muscle cell actin.	0.01
AB040888		Homo sapiens mRNA for KIAA1455 protein, partial cds	Function unknown	0.01
AA628980	Hs.192371:3	DSCR8	Function unknown	0.01
AI623351	Hs.172148:51	down syndrome critical region protein DSCR8 ESTs	Function unknown	0.01
AW614420	Hs.204354:383	ARHB	Function unknown	0.01
		ras homolog gene family, member B	RHO small monomeric GTPase, RHO protein signal transduction, peripheral plasma membrane protein. Ras-related GTP binding protein of the rho subfamily, member B; may regulate assembly of actin stress fibers and focal adhesions; very strongly similar to murine Arhb.	0.01
AA243499	Hs.104800:23	hypothetical protein FLJ10134	Highly similar to murine p19.5; are a membrane protein	0.01
AF251237	Hs.112208:16	GAGED2	GAGE genes are expressed in a variety of tumors and in some fetal and reproductive tissues. This gene is strongly expressed in Ewing's sarcoma, alveolar rhabdomyosarcoma and normal testis. The protein encoded by this gene contains a nuclear localization signal and shares a sequence similarity with other GAGE/PAGE proteins. Because of the expression pattern and the sequence similarity, this protein also belongs to a family of CT (cancer-testis) antigens.	0.01
		XAGE-1 protein		
AI970797	Hs.84859:16	ESTs	Function unknown	0.01
AF145713	Hs.61490:51	SCHIP1	Cytoplasm. Associates with the neurofibromatosis type 2 protein schwannomin (NF2); contains a coiled-coil domain Proteome	0.01

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
X78565	Hs.289114;173;Hs.74637:1	TNC hexabrachion (tenascin C, cytactin)	Cell adhesion, extracellular matrix, cell adhesion receptor, ligand binding or carrier. Hexabrachion (tenascin C), an extracellular matrix glycoprotein; has epidermal growth factor-like repeats	0.01
T97307	gb:ye53h05.s1 Soares fetal liver spleen 1NFLS Homo sapiens cDNA clone IMAGE:121497 3', mRNA sequence.		Function unknown	0.01
BE243845	Hs.75511:418	CTGF connective tissue growth factor	Cell motility, plasma membrane, soluble fraction, response to wounding, extracellular matrix, extracellular space, epidermal differentiation, cell growth and maintenance, insulin-like growth factor binding, insulin-like growth factor receptor binding protein. Connective tissue growth factor; binds IGF, may have a role in regulating normal and neoplastic cell growth	0.01
AW068302	Hs.182183;214;Hs.325474;172;Hs.283080:7	CALD1 caldesmon 1	Cytoskeleton, actin binding, calmodulin binding, tropomyosin binding. Protein of unknown function. Actomyosin regulatory protein, non-muscle form	0.01
AL133561	Hs.241428:5	DKFZP434B081 protein	Function unknown	0.01
BE313555	Hs.7252:158	RAI17 retinoic acid induced 17	Function unknown	0.02
X07820	Hs.2258:1	MMP10 matrix metalloproteinase 10 (MMP10; stromelysin 2)	Zinc binding, extracellular space, extracellular matrix, metalloendopeptidase, proteolysis and peptidolysis. Stromelysin 2; matrix metalloprotease that degrades connective tissue	0.02
AI973016	Hs.15725:77	IER5 Immediate early response 5	Function unknown. A related mouse gene may play an important role in mediating the cellular response to mitogenic signals.	0.02
AF084545		Homo sapiens versican Vint isoform, mRNA, partial cds	Function unknown	0.02
U41518	Hs.74602:146;Hs.767:1	AQP1 aquaporin 1 (channel-forming integral protein, 28kD)	Excretion, water transport, water transporter, integral plasma membrane protein. Aquaporin 1 (channel-forming integral protein); member of a family of water-transporters	0.02
Z11894		H.sapiens rearranged mRNA for immunoglobulin kappa chain (VNU)		0.02
AW138190	Hs.180248:8	ZNF124 zinc finger protein 124 (HZF-16)	DNA binding. C2H2 zinc-finger protein 124	0.02
BE086548	Hs.42346:83;Hs.6975:42	MYO22 myozenin 2	calcineurin-binding protein calsardin-1	0.02

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
W47196	Hs.166172:50	ARNT aryl hydrocarbon receptor nuclear translocator	Nucleus, transcription factor, transcription co-activator, transcription, DNA-dependent, protein-nucleus import, translocation, aryl hydrocarbon receptor nuclear translocator. Aryl hydrocarbon receptor nuclear translocator; used in receptor translocation from cytosol to nucleus	0.02
A1796870	Hs.54277:76	DXS9928E DNA segment on chromosome X (unique) 9928	Nucleus. Has many charged residues and a possible nuclear localization signal	0.02
X02761	Hs.287820:73,Hs.321592:1	FN1 fibronectin 1	Cell adhesion, cell motility, cell adhesion, soluble fraction, signal transduction, extracellular matrix, extracellular space, Fibronectin 1; member of family of proteins found in plasma and extracellular matrix	0.02
AW968613	Hs.78428:166	BNIP3 BCL2/adonovirus E1B 19kD-interacting protein 3	Anti-apoptosis, apoptosis inhibitor. Bcl2-related protein 3; binds antiapoptotic viral E1B 19 kDa protein and cellular Bcl2 protein	0.02
AW972565	Hs.32399:24	ESTs, Weakly similar to S51797 vasodilator-stimulated phosphoprotein [H.seplens]	Function unknown	0.02
AF045229	Hs.82280:81	RGS10 regulator of G-protein signalling 10	Regulator of G protein signalling (RGS) family members are regulatory molecules that act as GTPase activating proteins (GAPs) for G alpha subunits of heterotrimeric G proteins. RGS proteins are able to deactivate G protein subunits of the G1 alpha, G2 alpha and Gq alpha subtypes. They drive G proteins into their inactive GDP-bound forms.	0.02
AW953853	Hs.292833:19	PAEP progesterone-associated endometrial protein (placental protein 14, pregnancy-associated endometrial alpha-2-globulin, alpha uterine protein)	Developmental processes. Placental protein 14 (Glycodelin); member of lipocalin superfamily, highly similar to beta-lactoglobulins	0.02
U52426	Hs.74597:75,Hs.157615:3	STIM1 stromal interaction molecule 1	Integral plasma membrane protein, positive control of cell proliferation. Very strongly similar to murine Stim1; are a transmembrane stromal cell protein	0.02
F06700	Hs.7879:115	IFRD1 Interferon-related developmental regulator 1	Myoblast determination. Strongly similar to rat interferon-related developmental regulator 1; may play a role in muscle differentiation	0.02
A1798863	Hs.87191:8	ESTs	Function unknown	0.03
NA		C4001170:gl[6863176]b[AAF30402.1]AF109924_1 (AF109924) sulfatase 1 precursor [Helix poma		0.03
H52761	Hs.141475:24	Homo sapiens cDNA clone IMAGE:178663	Function unknown	0.03

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
BE546947	Hs.44276:43	HOXC10 homeo box C10	Embryogenesis and morphogenesis, positive control of cell proliferation, RNA polymerase II transcription factor. Homeobox C10, member of the homeobox developmental regulator family; binds with HOXA13 and HOXC13 to the Lamin B2 origin; ortholog of Drosophila Abdominal-B	0.03
AU076843	Hs.313:257,Hs.32991 0:1	SPP1. secreted phosphoprotein 1 (osteopontin, bone sialoprotein I, early T-lymphocyte activation 1)	Ossification, extracellular matrix, skeletal development. Osteopontin (bone sialoprotein); bone and blood vessel extracellular matrix protein involved in calcification and atherosclerosis	0.03
#(NOCAT)		NM_015902*:Homo sapiens prostasin induced protein (DD5), mRNA. VERSION NM_020967.1 GI		0.03
U20538	Hs.3280:20	CASP6 caspase 6, apoptosis-related cysteine protease	Induction of apoptosis, cysteine-type peptidase, proteolysis and peptidolysis. Caspase 6; a cysteine (thiol) protease; related to the ICE-subfamily of caspases	0.03
AA581602	Hs.41840:7	ESTs	Function unknown	0.03
AJ245210		gb:Homo sapiens mRNA for immunoglobulin gamma heavy chain variable region, partial, clone 1A-4C21.	Function unknown	0.03
X65965		H.sapiens SOD-2 gene for manganese superoxide dismutase		0.03
AI808770	Hs.30258:9	ESTs	Function unknown	0.03
BE388490	Hs.279663:51	PIR PirIn	Nucleus, transcription co-factor, transcription from Pol II promoter. Putative cofactor of the NF1/CTF1 transcriptional activator	0.03
AW581892	Hs.301434:104,Hs.32 8017:1	KIAA1387 KIAA1387 protein	Function unknown	0.03
U77534		Human clone 1A11 immunoglobulin variable region (VH5-D-JH4) gene, partial cds	Function unknown	0.03
AL034417	Hs.11169:194,Hs.109 58:1,Hs.74137:1	Gene 33/Mig-6	Function unknown	0.03
L10343	Hs.112341:96,Hs.196 8:1	Homo sapiens elafin precursor, gene, complete cds	Function unknown	0.03
AW518944	Hs.76325:80,Hs.2312 99:1	IGJ immunoglobulin J polypeptide, linker protein for immunoglobulin alpha and mu polypeptides	Linker protein for immunoglobulin alpha and mu polypeptides	0.03

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
W28729	Hs.236510:6	Human retina cDNA randomly primed sublibrary Homo sapiens cDNA, mRNA sequence	Function unknown	0.03
A1640160	Hs.74131:4	ARSE arylsulfatase E (chondrodysplasia punctata 1)	Arylsulfatase, skeletal development. Arylsulfatase E; likely involved in warfarin embryopathy.	0.03
U11862	Hs.75741:62	ABP1 amiloride binding protein 1 (amine oxidase (copper-containing))	Metabolism, peroxisome, amine oxidase, drug binding. Diamine oxidase (D-amino-acid oxidase histaminase, amiloride-binding protein); deaminates putrescine and histamine	0.03
AW295980	Hs.252741:3	ESTs	Function unknown	0.03
X59135	Hs.158110:4	H.sapiens mRNA for Immunoglobulin 0-81VL		0.03
BE466173	Hs.378794	Homo sapiens mRNA; cDNA DKFZp686N0118 (from clone DKFZp686N0118)	Function unknown	0.03
#(NOCAT)		Target Exon		0.03
A1354722	Hs.127216:24	hypothetical protein FLJ13465	Function unknown	0.04
M90464	Hs.169825:45,Hs.408:1	Human collagen type IV alpha 5 chain (COL4A5) gene, 5' end	Function unknown	0.04
AA829286	Hs.332053:48,Hs.336462:10	SAA1 serum amyloid A1	Inflammatory response, high-density lipoprotein. Member of the serum amyloid A protein family, member of high density apolipoproteins.	0.04
A1333771	Hs.82204:8,Hs.228363:1	ESTs	Function unknown	0.04
BE465867; NIM_014992	Hs.197751:66	DAAM1 dishevelled associated activator of morphogenesis 1	The protein encoded by this gene contains FH domains and belongs to a novel FH protein subfamily implicated in cell polarity, thought to function as a scaffolding protein.	0.04
BE616902	Hs.285313:145,Hs.4055:43	COPEB core promoter element binding protein	A transcriptional activator, capable of activating transcription approximately 4-fold either on homologous or heterologous promoters. The DNA binding and transcriptional activity of this protein, in conjunction with its expression pattern, suggests that this protein may participate in the regulation and/or maintenance of the basal expression of pregnancy-specific glycoprotein gene and possibly other TATA box-less genes.	0.04

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AA430373		gb:zw20711.s1 Soares ovary tumor NbHOT Homo sapiens cDNA clone IMAGE:769869 3' similar to gb:M63438 IG KAPPA CHAIN PRECURSOR V-III REGION (HUMAN);, mRNA sequence.	Function unknown	0.04
R27430	Hs.271565:3	ESTs	Function unknown	0.04
BE387335	Hs.283713:68	CTHRC1	Function unknown	0.04
AW264102	Hs.39168:16	collagen triple helix repeat containing 1	Function unknown	0.04
NA		ESTs	Function unknown	0.04
AW952323	Hs.129908:39	Target Exon	Function unknown	0.04
AA088177	Hs.172870:13	KIAA0591 protein	Function unknown	0.04
BE614567	Hs.19574:123	ESTs	Function unknown	0.04
		MGC5469	Function unknown	0.04
		hypothetical protein MGC5469		
AL078658	Hs.338207:139,Hs.146559:1	FRAP1	DNA repair, DNA recombination, cell cycle control, 1-phosphatidylinositol 3-kinase, inositol/phosphatidylinositol kinase, FKBP-rapamycin associated protein; phosphatidylinositol kinase that may mediate rapamycin inhibition of the cell cycle progression through G1	0.04
NM_002776	Hs.69423:46,Hs.275464:1	KLK10	Extracellular, serine-type peptidase. Putative serine protease	0.04
BE261944	Hs.118625:62	kalikrein 10 (KLK10) (PRSSL1) (nest1)	Energy pathways, secretory vesicle, cytochrome b5 reductase, secretory vesicle membrane, integral plasma membrane protein, Cytochrome b5b1; serves as a biological marker for adrenergic secretory vesicles	0.04
NM_006379	Hs.171921:50	CYB5b1	Drug resistance, immune response, cell growth and maintenance, Semaphorin E; member of a protein family involved in neuronal growth cone guidance	0.04
AI002238	Hs.11482:19	SEMA3C	Nucleus, mRNA splicing, mRNA processing, pre-mRNA splicing factor. May have a role in pre-mRNA splicing; contains arginine/serine-rich domain and an RRM domain	0.04
		sema domain, immunoglobulin domain (Ig), short basic domain, secreted, (semaphorin) 3C		
#(NOCAT)		SFRS11		
		splicing factor, arginine/serine-rich 11		
X81789	Hs.77897:149	ENSP00000231844*:Ecotropic virus integration 1 site protein.		
		SF3A3	Nucleus, spliceosome, mRNA splicing, mRNA processing, pre-mRNA splicing factor. Spliceosome-associated protein 3a, subunit 3; component of the essential heterotrimeric splicing factor SF3a; contains a zinc finger	0.04
		splicing factor 3a, subunit 3, 60kD		

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
NM_002122	Hs.198253:21	HLA-DQA1 major histocompatibility complex, class II, DQ alpha 1	Pathogenesis, class II major histocompatibility complex antigen. Alpha 1 chain of HLA-DQ1 class II molecule (Ia antigen); complex binds peptides and presents them to CD4+ T lymphocytes[Proteome Function unknown]	0.00
AB001914		Homo sapiens PACE4 gene, exon 23-25, complete cds	Function unknown	0.04
AA311919	Hs.69851:24	NOLA1 nucleolar protein family A, member 1 (H1ACA small nucleolar RNPs)	Involved in various aspects of rRNA processing and modification. Localize to the dense fibrillar components of nucleoli and to coiled (Cajal) bodies in the nucleus.	0.04
AI381750	Hs.283437:122,Hs.10 085:58	HTGN29 protein	Function unknown	0.04
#(NOCAT)		NM_000636*:Homo sapiens superoxide dismutase 2, mitochondrial (SOD2), mRNA, expression (RFY2), mRNA.	Mitochondrion, oxidative stress response, manganese superoxide dismutase. Manganese superoxide dismutase; intramitochondrial free radical scavenging enzyme; has strong similarity to murine Sod2.	0.04
AA292988	Hs.163800:25	ESTs	Function unknown	0.04
BE439580	Hs.75498:40	SCYA20 small inducible cytokine subfamily A (Cys-Cys), member 20	Chemokine, chemotaxis, immune response, signal transduction, extracellular space, cell-cell signalling, inflammatory response, antimicrobial humoral response. Cytokine A20 (exodus); chemotactic factor for lymphocytes, but not a chemotactic factor for monocytes	0.04
AI677897	Hs.76640:124	RGC32 RGC32 protein Target Exon	Cytoplasm, cell cycle regulator, regulation of CDK activity. Strongly similar to RGC-32.	0.04
#(NOCAT)		Homo sapiens cDNA clone IMAGE:245132	Function unknown	0.04
N72403		MMP12 matrix metalloproteinase 12 (macrophage elastase)	Function unknown	0.05
BE003054	Hs.1695:46	Human DNA sequence from clone 686P-19 on chromosome 6p12.3-21.2. Contains the gene for TFEB, an NPM1 (Nucleophosmin, Numatrin) pseudogene and the MDF1 gene for MyoD family inhibitor (myogenic repressor I-MF). Contains ESTs, STSs, GSSs and two putative CpG islands, complete sequence	Zinc binding, cell motility, macrophage elastase, extracellular matrix, proteolysis and peptidolysis. Matrix metalloprotease; degrades elastin	0.05
AL035588	Hs.153203:26,Hs.233 91:1		Function unknown	0.05
AI080491	Hs.93270:3	ESTs, Moderately similar to S85657 alpha-1C- adrenergic receptor splice form 2 [H.sapiens]	Function unknown	0.05

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AW770994	Hs.30340:125	hypothetical protein KIAA1165	Function unknown	0.05
H24177	Hs.75262:69,Hs.2389 12:1	CTSO cathepsin O	Cysteine-type endopeptidase, proteolysis and peptidolysis. Cathepsin O; cysteine (thiol) protease	0.05
AF146781	Hs.20450:29	BCM-like membrane protein precursor	Function unknown	0.05
NM_001955	Hs.2271:45,Hs.306:1	EDN1 endothelin 1	Circulation, peptide hormone, soluble fraction, signal transduction, extracellular space, cell-cell signalling, blood pressure regulation, positive control of cell proliferation, Preproendothelin 1; precursor of the hormone endothelin 1	0.05
A1680737	Hs.259068:204,Hs.32 6198:1	TCF4 transcription factor 4	Nucleus. RNA polymerase II transcription factor, transcription regulation from Pol II promoter. Transcriptional activator; interacts with ITF1 (TCF3); contains basic helix-loop-helix domain Proteome	0.05
A1752666	Hs.76669:183	NNMT nicotinamide N-methyltransferase	Nicotinamide N-methyltransferase; catalyzes the N-methylation of nicotinamide and other pyridines, structurally-related drugs and xenobiotics Proteome	0.05
AA505445	Hs.300697:21	IGHG3 immunoglobulin heavy constant gamma 3 (G3m marker)	Constant region of heavy chain of IgG3	0.05
BE246649; NM_003955	Hs.345728	SOCS3 STAT induced STAT-inhibitor 3; suppressor of cytokine signalling 3	suppression of IL-6 mediated signalling	0.02
M86849	Hs.323733:62,Hs.300 816:5	GJB2 gap junction protein, beta 2, 26kD (connexin 26)	Hearing, connexon, plasma membrane, connexon channel, cell-cell signalling, small molecule transport. Connexin 26; gap junction protein expressed in various tissues including cochlea.	0.00
AW863419	Hs.155223:20	STC2 stanniocalcin 2	Peptide hormone, cell-cell signalling, glycopeptide hormone, nutritional response pathway, cell surface receptor linked signal transduction. Stanniocalcin 2; may regulate metal ion homeostasis and inhibits phosphate uptake. Function unknown	0.00
BE298665	Hs.14846:132	Homo sapiens mRNA; cDNA DKFZp564D016 (from clone)	Function unknown	0.00
AK000637	Hs.46824:11	HSPC043 HSPC043 protein	Function unknown	0.00
BE077546	Hs.31447:27	ESTs, Moderately similar to A46010 X-linked retinopathy protein [H.sapiens]	Function unknown	0.00
T97307		gb:ye53h05.s1 Soares fetal liver spleen 1NFLS Homo sapiens cDNA clone IMAGE:121497 3';	Function unknown	0.00

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
		mRNA sequence.		
R24601	Hs.108300:46	Homo sapiens adenylosuccinate synthetase isozyme (ADSS) mRNA, complete cds	Function unknown	0.00
BE090176	Hs.179902:95	Interim-CDw92 antigen	choline transporter-like protein	0.00
AA393907	Hs.97179:22	ESTs	Function unknown	0.00
V28729	Hs.236510:6	Homo sapiens mRNA; cDNA DKFZp666D074 (from clone DKFZp666D074)	Function unknown	0.00
BE313754	Hs.13350:52	Homo sapiens mRNA; cDNA DKFZp586D0918	Function unknown	0.01
AW673081	Hs.54828:9	ESTs	Function unknown	0.01
AA366894	Hs.94011:42;Hs.7744:2;Hs.231043:1	HCA4 Hepatocellular carcinoma-associated protein HCA4	Function unknown	0.01
L08239	Hs.5326:11	MG61 Porcupine	amino acid system N transporter 2;	0.01
BE397649	Hs.94109:40	Homo sapiens cDNA FLJ34399 fis, clone HCHON2001359	Function unknown	0.01
NM_012317	Hs.45231:36	LDOC1 Leucine zipper, down-regulated in cancer 1	Nucleus, negative control of cell proliferation. Nuclear protein; contains a leucine zipper-like motif	0.01
NM_000947	Hs.74519:20	PRIM2A primase, polypeptide 2A (58kD)	DNA primase. DNA replication, priming, alpha DNA polymerase-primase complex. Subunit of DNA primase polypeptide 2A; part of the DNA polymerase alpha-primase complex	0.01
AJ250562	Hs.82749:133	Homo sapiens partial TM4SF2 gene for tetraspanin protein, exon 1 and joined CDS	Function unknown	0.01
AL040183	Hs.123484:24;Hs.326906:1	Homo sapiens mRNA; cDNA DKFZp686E1934 (from clone DKFZp686E1934)	Function unknown	0.01
BE207573	Hs.83321:32	NMB neuromedin B	Peptide hormone, soluble fraction, signal transduction, cell-cell signalling. Precursor of neuromedin B, a C-terminally amidated peptide hormone; similar to bombesin	0.01
BE564162	Hs.250820:45	FLJ14827 hypothetical protein FLJ14827	Function unknown	0.01

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
BE439580	Hs.75498:40	SCYA20 Small inducible cytokine subfamily A (Cys-Cys), member 20	Chemokine, chemotaxis, immune response, signal transduction, extracellular space, cell-cell signalling, inflammatory response, antimicrobial humoral response. Cytokine A20 (exodus); chemotactic factor for lymphocytes, but not a chemotactic factor for monocytes	0.01
AW067800	Hs.155223:52	STC2 stanniocalcin 2	Peptide hormone, cell-cell signalling, glycopeptide hormone, nutritional response pathway, cell surface receptor linked signal transduction. Stanniocalcin 2; may regulate metal ion homeostasis and inhibits phosphate uptake.	0.01
AA569756	Hs.87803:10	Homo sapiens cDNA FLJ30156 fis, clone BRACE2000487	Function unknown	0.01
AW138180	Hs.180248:8	ZNF124 zinc finger protein 124 (HZF-16)	DNA binding. C2H2 zinc-finger protein 124	0.01
AF126245	Hs.14791:48	ACAD8 acyl-Coenzyme A dehydrogenase family, member 8	Lipid metabolism, acyl-CoA dehydrogenase. Member of the acyl-Coenzyme A dehydrogenase family; alpha,beta-dehydrogenates acyl-CoA esters	0.01
L10343	Hs.112341:98,Hs.1988:1	Homo sapiens elafin precursor, gene, complete cds	elastase-specific inhibitor in bronchial secretions	0.01
NM_002514	Hs.235935:38	NOV nephroblastoma overexpressed gene	Insulin-like growth factor receptor binding protein. Insulin-like growth factor binding protein; may play a role in nephrogenesis	0.01
AI863735	Hs.186755:3	ESTs	Function unknown	0.01
NM_005397	Hs.18426:160,Hs.248780:1	PODXL podocalyxin-like	Integral plasma membrane protein. Transmembrane protein similar to rodent podocalyxins	0.01
W26391	Hs.301206:100	KIF3B kinesin family member 3B	Plus-end kinesin, microtubule motor, anterograde axon cargo transport, plus-end-directed kinesin ATPase, determination of left-right asymmetry. Similar to murine Kif3b; may have a role in intracellular organelle transport, may act in left-right determination in embryogenesis; are a microtubule-associated motor protein	0.01
H15474	Hs.132898:156	FADS1 fatty acid desaturase 1	C-5 sterol desaturase, fatty acid desaturation, integral membrane protein. Delta-5 desaturase; catalyzes production of polyenoic fatty acids such as arachidonic acid	0.01
U51188	Hs.173824:108	TDG Thymine-DNA glycosylase	DNA repair, nucleoplasm, damaged DNA binding, base-excision repair, G/T-mismatch-specific thymine-DNA glycosylase. Thymine-DNA glycosylase; excises uracil and thymine from mispairs with guanine	0.01
AA243499	Hs.104800:23	FLJ10134 hypothetical protein FLJ10134	Highly similar to murine p18.5; are a membrane protein	0.01
AW408807	Hs.34497:46	FLJ22118 hypothetical protein FLJ22118	Function unknown	0.01

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AI738719	Hs.198427:98	HK2 Hexokinase 2	Hexokinase, cell cycle control, glucose catabolism, glucose metabolism, mitochondrial outer membrane. Hexokinase II; converts aldo- and keto-hexose sugars to the hexose-6-phosphate	0.01
AB040888	Hs.41793:110	Homo sapiens mRNA for KIAA1455 protein, partial cds	Function unknown	0.01
BE313077	Hs.93135:40,Hs.228357:1	Homo sapiens cDNA FLJ39971 fis, clone SPLEN2028066	Function unknown	0.01
AI677897	Hs.76640:124	RGC32 RGC32 protein	Cytoplasm, cell cycle regulator, regulation of CDK activity. Strongly similar to RGC-32	0.01
C14898	Hs.192986:5	ESTs	Function unknown	0.01
AI821730	Hs.116524:7	Homo sapiens cDNA FLJ35800 fis, clone TEST12005933	Function unknown	0.01
AF007393	Hs.177574:111	PRKRIR protein-kinase, Interferon-inducible double stranded RNA dependent inhibitor, repressor of (P58 repressor)	Stress response, protein binding, signal transduction, translational regulation, negative control of cell proliferation. Regulates Interferon-induced protein kinase PKR (PRKR) activity by binding and inhibiting the PKR-regulator P58IPK (PRKRI)	0.01
H65423	Hs.17631:42	DKFZP434E2135 hypothetical protein DKFZp434E2135	Function unknown	0.01
N46243	Hs.110373:28	ESTs, Highly similar to T42626 secreted leucine-rich repeat-containing protein SLIT2 - mouse (fragment) [M.musculus]	Function unknown	0.01
AA095971	Hs.198793:56,Hs.308674:7	Homo sapiens cDNA: FLJ22463 fis, clone HRC10126	Function unknown	0.01
U20350	Hs.78913:33	CX3CR1 chemokine (C-X3-C) receptor 1	Virulence, chemotaxis, coreceptor, cell adhesion, plasma membrane, chemokine receptor, response to wounding, cellular defense response, integral plasma membrane protein, G-protein linked receptor protein signalling pathway. CX3C chemokine receptor; G protein-coupled receptor, mediates leukocyte migration and adhesion, binds the CX3C chemokine fractalkine and signals through a pertussis toxin sensitive G-protein	0.01
NM_005756	Hs.184942:18	GPR64 G protein-coupled receptor 64	Spermatogenesis, G-protein linked receptor, integral plasma membrane protein, G-protein linked receptor protein signalling pathway. Member of the G protein-coupled receptor family	0.01
D19589	Hs.13453:87	FLJ14753 hypothetical protein FLJ14753	Function unknown	0.02
AW957446	Hs.301711:74	ESTs	Function unknown	0.02

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AW294647	Hs.233634:40	C20orf39 chromosome 20 open reading frame 39	Function unknown	0.02
BE159718	Hs.85335:46	Homo sapiens, clone IMAGE:4513159, mRNA	Function unknown	0.02
AI888490	Hs.55902:22	EDG3 endothelial differentiation, sphingolipid G-protein-coupled receptor, 3	Lipid binding, plasma membrane, inflammatory response, G-protein linked receptor, embryogenesis and morphogenesis, integral plasma membrane protein, positive control of cell proliferation, cytosolic calcium ion concentration elevation, G-protein linked receptor protein signalling pathway. Lysophingolipid receptor, a G protein-coupled receptor; activates calcium flux and serum response element driven transcription	0.02
AA022569	Hs.29802:35,Hs.271785:1	ESTs	Function unknown	0.02
BE147740	Hs.104558:21	ESTs, Moderately similar to hypothetical protein FLJ20378 [Homo sapiens]	Function unknown	0.02
AI798863	Hs.87191:8	ESTs	Function unknown	0.02
BE464341	Hs.21201:18	Interim-DKFZP566B0848: nectin 3	Low similarity to PVRL1; are a membrane glycoprotein; contains an immunoglobulin (Ig) domain	0.02
AL080235	Hs.35881:34,Hs.289068:1	RIS1 Ras-induced senescence 1	Rat brain specific binding protein	0.02
AI557212	Hs.17132:102,Hs.330782:1	ESTs	Function unknown	0.02
X75208	Hs.2913:41	EPHB3 EPHB3	Signal transduction, integral plasma membrane protein, transmembrane receptor protein tyrosine kinase. Eph-related receptor tyrosine kinase B3	0.02
AA628980	Hs.192371:3	DSCR8 Down syndrome critical region protein DSCR8	Melanoma-testis-associated protein 2	0.02
BE242587	Hs.118651:39	HHEX hematopoietically expressed homeobox	Nucleus, DNA binding, transcription factor, developmental processes, antimicrobial humoral response. Member of the homeodomain family of DNA binding proteins; may regulate gene expression, morphogenesis, and differentiation	0.02
NIM_005512	Hs.151641:65	GARP glycoprotein A repetitions predominant	Integral plasma membrane protein. Putative transmembrane cell surface protein; has an extracellular domain comprised largely of leucine-rich repeats	0.02
AW953853	Hs.292833:19	PAEP progesterone-associated endometrial protein (placental protein 14, pregnancy-associated endometrial alpha-2-globulin, alpha uterine	Developmental processes. Placental protein 14 (Glycodelin); member of lipocalin superfamily, highly similar to beta-lactoglobulins	0.02

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AU076611	Hs.154672:122	protein) MTHFD2 methylene tetrahydrofolate dehydrogenase (NAD dependent), methenyltetrahydrofolate cyclohydrolase	Mitochondrion, electron transporter, methenyltetrahydrofolate cyclohydrolase, methenyltetrahydrofolate dehydrogenase. NAD-dependent methylene tetrahydrofolate dehydrogenase-cyclohydrolase; may provide formyltetrahydrofolate for formylmethionyl tRNA synthesis; involved in initiation of mitochondrial protein synthesis	0.02
AW968613	Hs.79428:166	BNIP3 BCL2/adenovirus E1B 19kD-interacting protein 3	Anti-apoptosis, apoptosis inhibitor. Bcl2-related protein 3; binds antiapoptotic viral E1B 19 kDa protein and cellular Bcl2 protein	0.02
AL353944	Hs.50115:14	Homo sapiens mRNA: cDNA DKFZp761J1112 (from clone DKFZp761J1112)	Function unknown	0.02
BE614149	Hs.20814:29,Hs.306626:27	LOC51072: C21orf19-like protein	Function unknown	0.02
AA292998	Hs.163900:25	ESTs	Highly similar to winged helix/forkhead transcription factor	0.02
H12912	Hs.274691:138	AK3 adenylyate kinase 3	Nucleoside, nucleotide and nucleic acid metabolism. Adenylyate kinase 3; strongly similar to murine AK4	0.02
AA188763	Hs.36793:4	SLC12A8 solute carrier family 12 (potassium/chloride transporters), member 8	Solute carrier family 12 (potassium/chloride transporters), member 8	0.02
AK000596	Hs.3618:56	HPICAL1 hippocalcin-like 1	Calcium-binding protein with similarity to hippocalin (human HPCA); expressed only in the brain.	0.02
A1970797	Hs.64859:16	ESTs	Function unknown	0.02
AW519204	Hs.40808:22	ESTs	Function unknown	0.02
Z42387	Hs.83883:114	TMEPA1 transmembrane, prostate androgen induced RNA	Function unknown	0.02
AF145713	Hs.81490:51	SCHIP1 schwannomin-interacting protein 1	Cytoplasm. Associates with the neurofibromatosis type 2 protein schwannomin (NF2); contains a coiled-coil domain	0.02
AA972412	Hs.13755:41	FBXW2 f-box and WD-40 domain protein 2	Protein modification, ubiquitin-protein ligase, proteolysis and peptidolysis, ubiquitin conjugating enzyme. F-box and WD-40 domain protein 2; putative SCF ubiquitin ligase subunit involved in protein degradation; contains a WD-40 domain and an F-box Member of the ADP-ribosylation factor (ARF) family; putative GTP-binding protein involved in protein trafficking	0.02
AK001564	Hs.104222:139,Hs.296267:4	Homo sapiens cDNA FLJ10702 fs, clone NT2RP3000759, weakly similar to ADP-RIBOSYLATION FACTOR		0.02

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AW959861	Hs.280943:28	ESTs	Function unknown	0.02
BE313555	Hs.7252:158	RAI17 retinoic acid induced 17	Function unknown	0.02
W25005	Hs.24395:189	zb87e02.r1 Soares fetal lung NibHL19W Homo sapiens cDNA clone IMAGE:308668 5', mRNA sequence ESTs	Function unknown	0.02
AI193356	Hs.160316:3	ESTs	Function unknown	0.02
AF111106	Hs.3382:223	PPP4R1 Protein phosphatase 4, regulatory subunit 1	Protein phosphatase	0.02
AI130740	Hs.6241:116	PIK3R1 phosphoinositide-3-kinase, regulatory subunit, polypeptide 1 (p85 alpha)	A family of enzymes that phosphorylate the 3'-hydroxyl of phosphatidylinositol (PtdIns).	0.02
AA985190	Hs.246875:42	FLJ20059 hypothetical protein FLJ20059	Contains four Kelch motif domains	0.02
BE221880	Hs.268555:144	XRN2 5'-3' exoribonuclease 2	Nucleus, nuclease, recombination, RNA catabolism, RNA processing, 5'-3' Exoribonuclease; similar to Schizosaccharomyces pombe Dhp1p	0.03
AF084545		Homo sapiens versican Vint isoform, mRNA, partial cds	Function unknown	0.03
R26584	Hs.267993:43	TAPBP-R: TAP binding protein related	Has low similarity to TAPBP (Tapasin); contains two immunoglobulin (Ig) domains Proteome	0.03
AW247380	Hs.12124:116	ELAC2 elacC homolog 2 (E. coli)	putative prostate cancer susceptibility protein	0.03
AA364261	Hs.131365:7	ESTs	Weakly similar to T31613 hypothetical protein Y50E8A.I - Caenorhabditis elegans [C.elegans]	0.03
U25849	Hs.75393:141	ACP1 Human red cell-type low molecular weight acid phosphatase (ACP1) gene, exon 6 and 7, complete cds	Acid phosphatase	0.03
AF262992	Hs.123159:14	SPAG4 Sperm associated antigen 4	Spermatogenesis, structural protein. Sperm associated antigen 4; predicted ortholog of rat SPAG4, which interacts with rat ODF27, the 27kDa outer dense fiber protein of elongating spermatids	0.03
AW342140	Hs.182545:1	ESTs, Weakly similar to POL2_MOUSE Retrovirus-related POL polypeptide	Function unknown	0.03
AL133572	Hs.199009:58	PCCX2 protein containing CXXC domain 2	DNA-binding protein with PHD finger and CXXC domain, is regulated by proteolysis.	0.03

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AI497778	Hs.20509:4	HBXAP Hepatitis B virus x associated protein	Weakly similar to Drosophila CG8677	0.03
AI745379	Hs.42911:31	TAF13 TAF13 RNA polymerase II, TATA box binding protein (TBP)-associated factor, 18 kD	TFIID complex, protein binding, transcription factor, general RNA polymerase II transcription factor. TBP-associated factor K; component of TFIID complexes containing TAF130 (TAF2H)	0.03
U51712	Hs.13775:135	LAGY: lung cancer-associated Y protein	The protein encoded by this gene is a lung cancer associated protein. The function of the protein is not known. Multiple alternatively spliced transcript variants have been described for this gene but some of their full length sequence has not been determined.	0.03
AW375974	Hs.156704:4	ESTs	Function unknown	0.03
AF251237	Hs.112208:16	GAGED2 G antigen, family D, 2	GAGE genes are expressed in a variety of tumors and in some fetal and reproductive tissues. This gene is strongly expressed in Ewing's sarcoma, alveolar rhabdomyosarcoma and normal testis. The protein encoded by this gene contains a nuclear localization signal and shares a sequence similarity with other GAGE/PAGE proteins. Because of the expression pattern and the sequence similarity, this protein also belongs to a family of CT (cancer-testis) antigens.	0.03
NM_000636		Homo sapiens superoxide dismutase 2, mitochondrial (SOD2), mRNA, expression (RFX2), mRNA.	Mitochondrion, oxidative stress response, manganese superoxide dismutase. Manganese superoxide dismutase; intramitochondrial free radical scavenging enzyme; has strong similarity to murine Sod2.	0.02
AA130986	Hs.271627:1	ESTs	Function unknown	0.01
AA216363	Hs.262958:48,Hs.327737:2	DKFZP434B044 hypothetical protein DKFZP434B044	Function unknown	0.01
AA628980	Hs.192371:3	DSCR8 down syndrome critical region protein DSCR8	Function unknown	0.00
AA811857	Hs.220913:9	Homo sapiens cDNA FLJ40827 fis, clone TRACH2011500	Function unknown	0.02
AA897108		gb:am08a06.s1 Soares_NFL_T_GBC_S1 Homo sapiens cDNA clone 3', mRNA sequence	Function unknown	0.01
AB040888	Hs.41793:110	Homo sapiens mRNA for KIAA1455 protein, partial cds	Function unknown	0.02

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
AF212225	Hs.283693:104	Homo sapiens BMD22 mRNA, complete cds	Function unknown	0.02
A1089575	Hs.9071:52	ESTs	Function unknown	0.02
A1282028	Hs.25205:10	ESTs	Function unknown	0.02
A1368826	Hs.30654:15	FLJ10849: hypothetical protein FLJ10849	Moderately similar to members of the septin family	0.02
A1718702	Hs.308026:11, Hs.194490:6	HLA-DRB3 major histocompatibility complex, class II, DR beta 5	Signal transduction, integral plasma membrane protein, class II major histocompatibility complex antigen. Beta 3 chain of HLA-DR; subunit of MHC class II molecule, complex binds peptides and presents them to CD4+ T lymphocytes	0.02
A1827248	Hs.224398:3	Homo sapiens cDNA FLJ11469 fis, clone HEMBA1001658	Function unknown	0.01
AK002039	Hs.26243:38	MRV1 murine retrovirus integration site 1 homolog	Oncogenesis, tumor suppressor, endoplasmic reticulum membrane. Similar to human MLRP; may act as a tumor suppressor	0.02
AL109791	Hs.241559:3	Homo sapiens mRNA full length insert cDNA clone EUROMAGE 151432	Function unknown	0.00
AW090198	Hs.4779:29	LOC127829: hypothetical protein BC015408	Function unknown	0.01
AW296454	Hs.24743:92	FLJ20171: hypothetical protein FLJ2017	Contains three RNA recognition motifs (RRM, RBD, or RNP)	0.02
AW445034	Hs.256578:4	ESTs	Function unknown	0.00
AW452948	Hs.257631:3	ESTs	Function unknown	0.01
AW470411	Hs.288433:27	HNT: neurotrimin	Cell adhesion, neuronal cell recognition, integral plasma membrane protein. Neurotrimin; may function as a GPI-anchored neural cell adhesion molecule; member of the immunoglobulin superfamily	0.02
AW885727	Hs.301570:22	FST follistatin	Developmental processes. Follistatin; inhibits the release of follicle-stimulating hormone (FSH)	0.01
AW970859	Hs.313503:4	ESTs	Function unknown	0.02
AW979189	Hs.283367:3	ESTs	Function unknown	0.01

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
BE165866	Hs.83623:66	Human XIST, coding sequence "a" mRNA (locus DXS399E)	XIST mRNA	0.01
BE175582	gb:RC5-HT0580-100500-022-C01 HT0580 Homo sapiens cDNA, mRNA sequence		Function unknown	0.01
BE242587	Hs.118651:39	HHEX hematopoietically expressed homeobox	Nucleus, DNA binding, transcription factor, developmental processes, antimicrobial humoral response. Member of the homeodomain family of DNA binding proteins; may regulate gene expression, morphogenesis, and differentiation	0.01
BE271927	Hs.87385:31, Hs.3079 40:4	LOC115416: hypothetical protein BC012331	Function unknown	0.01
BE439580	Hs.75498:40	SCYA20 small inducible cytokine subfamily A (Cys-Cys), member 20	Chemokine, chemotaxis, immune response, signal transduction, extracellular space, cell-cell signalling, inflammatory response, antimicrobial humoral response. Cytokine A20 (exodus); chemotactic factor for lymphocytes, but not a chemotactic factor for monocytes	0.02
BE464016	Hs.238956:35	Homo sapiens cDNA FLJ37793 fs, clone BRHIP3000473	Function unknown	0.02
D63216	Hs.153684:137	FRZB frizzled-related protein	Membrane, extracellular, skeletal development. Frizzled-related protein; similar to frizzled family of receptors	0.02
F34856	Hs.292457:120	Homo sapiens, clone MGC:16362 IMAGE:3927795, mRNA, complete cds	Function unknown	0.02
M83822	Hs.62354:112	LRBA LPS-responsive vesicle trafficking, beach and anchor containing	May mediate protein-protein interactions; contains two WD domains (WD-40 repeats) and a beige/BEACH domain	0.02
N33937	Hs.10336:6	ESTs	Function unknown	0.01
N49068	Hs.93966:4	ESTs	Function unknown	0.01
N51357	Hs.260855:62	NSE1; NSE1	Function unknown	0.02
N80486	Hs.39911:17	Homo sapiens mRNA for FLJ00089 protein, partial cds	Function unknown	0.02
NM_000954	Hs.8272:265, Hs.3323 55:1	PTGDS prostaglandin D2 synthase (21kD, brain)	Membrane, prostaglandin-D synthase. Glutathione-independent prostaglandin D2 synthase; membrane associated, catalyzes synthesis of prostaglandin D; member of the lipocalin family of transporters	0.02
NM_005756	Hs.184942:18	GPR64 G protein-coupled receptor 64	Spermatogenesis, G-protein linked receptor, integral plasma membrane protein, G-protein linked receptor protein signalling pathway. Member of the G protein-coupled receptor family	0.02

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
NM_016652	Hs.268281:61	CRNKL1 Ctn, crooked neck-like 1 (Drosophila)	Function unknown	0.02
R26584	Hs.267993:43	TAPBP-R: TAP binding protein related	Has low similarity to TAPBP (Tapasin); contains two immunoglobulin (Ig) domains	0.01
R31178	Hs.287820:6	FN1 fibronectin 1	Cell adhesion, cell motility, cell adhesion, soluble fraction, signal transduction, extracellular matrix, extracellular space, Fibronectin 1; member of family of proteins found in plasma and extracellular matrix	0.02
W05391	Hs.83623:8	Homo sapiens cDNA FLJ30298 fs, clone BRACE2003172	Function unknown	0.02
W25005	Hs.24395:199	zb67e02.r1 Soares_fetal_lung_NbHL19W Homo sapiens cDNA clone IMAGE:308666 5', mRNA sequence	Function unknown	0.01
W45393	Hs.55888:15	ATF7 activating transcription factor 7	Transcription factor, Leucine zipper DNA-binding protein; recognizes a cAMP response element (CRE), involved in the regulation of adenovirus E1a-responsive and cellular cAMP-inducible promoters	0.02
W68815	Hs.301885:20	Homo sapiens cDNA FLJ33794 fs, clone CTONG1000009	Function unknown	0.01
X65965		H. sapiens SOD-2 gene for manganese superoxide dismutase	Mitochondrion, oxidative stress response, manganese superoxide dismutase. Manganese superoxide dismutase; intramitochondrial free radical scavenging enzyme; has strong similarity to murine Sod2.	0.01
X76732	Hs.3164:58	NUCB2 nucleobindin 2	Cytosol, DNA binding, plasma membrane, calcium binding, extracellular space, Nucleobindin 2; may bind DNA and calcium; has DNA-binding and EF-hand domains, and a leucine-zipper	0.02
Z45051	Hs.22820:25	C20orf103 chromosome 20 open reading frame 103	Low similarity to a region of murine Lamp1/Proteome	0.02

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	P value
c. downregulated genes				
NM_022117	Hs.136164:23	SE20-4, cutaneous T-cell lymphoma-associated tumor antigen se20-4se20-4	Cutaneous T-cell lymphoma-associated tumor antigen se20-4se20-4; differentially expressed nucleolar TGF-beta1 target protein (DENTT); also known as CDA1	0
NM_005460	Hs.24948:32, Hs.300445:4	SNCAIP, synuclein, alpha interacting protein (synphilin)	Cytoplasm, pathogenesis, protein binding. Synphilin-1; promotes formation of cytosolic inclusions in neurons (SNCAIP). Synuclein alpha interacting protein contains several protein-protein interaction domains and interacts with alpha synuclein in neurons. Mutations of SNCAIP have been linked to Parkinson disease.	0
NM_002387	Hs.1345:5	MCC, mutated in colorectal cancers	Receptor, signal transduction, tumor suppressor. Similar to the G protein-coupled m3 muscarinic acetylcholine receptor. MCC is a candidate for the putative colorectal tumor suppressor gene. The MCC gene product are involved in early stages of colorectal neoplasia in both sporadic and familial tumors.	0
A1745249 A1694200	Hs.23650:30 Hs.356620, Hs.227913:11	Homo sapiens, clone MGC:9889 IMAGE:3888330 ESTs	Function unknown Function unknown	0.0009 0.0442

Table 2
Genes having modified expression in serous ovarian cancer relative to normal ovarian tissue

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
M25809	Hs.64173	ATP6V1B1, ATPase, H ⁺ transporting, lysosomal 56/58kD, V1 subunit B, isoform 1 (Renal tubular acidosis with deafness)	Subunit B1 (beta subunit) of a vacuolar-type H ⁺ -ATPase 1; apical proton pump that mediates distal nephron acid secretion	1082.30
AW959311	Hs.172012	DKFZP434J037: hypothetical protein DKFZp434J037	Function unknown	227.83
H16423	Hs.82885	Homo sapiens mRNA; cDNA DKFZp313F0317 (from clone DKFZp313F0317)	Function unknown	74.54
AI733848	Hs.71835	ZNF339, zinc finger protein 339	Zinc finger protein	55.13
AW055308	Hs.31803	NAC1, transcriptional repressor NAC1	Function unknown	52.63
AF034102	Hs.32951	SLC29A2, solute carrier family 29 (nucleoside transporters), member 2	Nitrobenzylthioinosine-insensitive equilibrative nucleoside transporter 2; may act in the uptake of purine and pyrimidine nucleosides	44.34
AI791805	Hs.85549	FLJ20273: RNA-binding protein	Contains four RNA recognition motifs (RRM, RBD, or RNP)	43.21
AW296454	Hs.24743	FLJ20171: hypothetical protein FLJ20171	Contains three RNA recognition motifs (RRM, RBD, or RNP)	38.91
Z43989	Hs.82141	Human clone 23612 mRNA sequence	Function unknown	37.89
AL043980	Hs.7886	PEL11, pellino homolog 1 (Drosophila)	Pellino protein	35.20
BE514982	Hs.38991	S100A2, S100 calcium binding protein A2	S100 calcium-binding protein A2; Interacts with target proteins to link extracellular stimuli and cellular responses; member of the S100 tissue/cell specific Ca ²⁺ -binding protein family	34.53
AI811807	Hs.108646	Target Exon Homo sapiens cDNA FLJ12534 fis, clone NT2RM4000244	Function unknown	34.02
U90441	Hs.3622	P4H-A2, procollagen-proline, 2-oxoglutarate 4-dioxygenase (proline 4-hydroxylase), alpha polypeptide II	Function unknown	32.34
T98226	Hs.171952	OCLN, occludin	Alpha 2 subunit of prolyl 4-hydroxylase; catalyzes the formation of 4-hydroxyproline in collagens	32.24
			This gene encodes an integral membrane protein which is located at tight junctions. This protein are involved in the formation and maintenance of the tight junction.	31.56

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
R35343	Hs.24988	Human DNA sequence from clone RP1-233G16 on chromosome Xq22.1-23. Contains the 5' part of a novel gene, ESTs, STSs, GSSs and a putative CpG island		31.22
BE247295	Hs.78452	SLC20A1, solute carrier family 20 (phosphate transporter), member 1	Sodium-dependent phosphate symporter; acts as a cell-surface receptor for gibbon ape leukemia virus	30.16
AB037734	Hs.4983	PCDH19, protocadherin	Protocadherin	29.90
AF212223	Hs.25010	C5000394*:g 12737280 ref XP_006882.2 keratin 18 [Homo sapiens]] 6633	Function unknown	29.30
AA026566	Hs.21943	Homo sapiens BM025 mRNA, complete cds	Function unknown	28.85
X14008	Hs.234734	NIF3L1, NIF3 (Ngg1 interacting factor 3, S.pombe homolog)-like 1	Amyotrophic lateral sclerosis 2 (juvenile) chromosome region, candidate 1	27.73
AA570256	Hs.286049	Human lysozyme gene (EC 3.2.1.17)	Lysozyme	27.66
AA137152		LOC116238: hypothetical protein BC014072	Function unknown	27.52
BE621807		PSA, phosphoserine aminotransferase	The protein encoded by this gene is likely a phosphoserine aminotransferase, based on similarity to proteins in mouse, rabbit, and Drosophila. Alternative splicing of this gene results in two transcript variants encoding different isoforms.	25.57
AB041036	Hs.57771	TM4SF1, transmembrane 4 superfamily member 1	L6 antigen; member of the transmembrane 4 superfamily (TM4SF)	25.40
F13386	Hs.7888	KLK11, kallikrein 11	Trypsin-like serine protease; has serine protease activity	25.05
AA158177	Hs.118722	Homo sapiens clone 23736 mRNA sequence	Function unknown	22.50
		FUT8, fucosyltransferase 8 (alpha (1,6) fucosyltransferase)	N-linked glycosylation, oligosaccharide biosynthesis, glycoprotein 6-alpha-L-fucosyltransferase, Alpha(1,6)fucosyltransferase (GDP-L-Fuc:N-acetyl-beta-D-glucosaminide:alpha1-6 fucosyltransferase); transfers fucose to N-linked type complex glycopeptides from GDP-Fuc; functions in asparagine-linked glycoprotein oligosaccharide synthesis	21.90
BE267045	Hs.75064	TBCC, tubulin-specific chaperone c	Tubulin-specific chaperone c; cofactor in the folding pathway of beta-tubulin, mediates the release of beta-tubulin polypeptides committed to the native state	21.49
		NM_005936:Homo sapiens myeloid/lymphoid or mixed-lineage leukemia (t(11q23) (MLL1-4)) homolog; translocated to, 4 (MLLT4), mRNA.	Function unknown	20.46

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
AA150864	Hs.790	MGST1, microsomal glutathione S-transferase 1	Microsome, glutathione transferase, Microsomal glutathione S-transferase; catalyzes the conjugation of glutathione to electrophilic compounds; member of a family of detoxication enzymes.	20.35
AW955632	Hs.66606	EST367702 MAGE resequences, MAGD Homo sapiens cDNA, mRNA sequence	Function unknown	20.26
AW637046	Hs.6527	QV1-LT0037-150200-069-609 LT0037 Homo sapiens cDNA, mRNA sequence	Function unknown	19.60
AA286887	Hs.24724	MFHAS1, malignant fibrous histiocytoma amplified sequence 1	The primary structure of its product includes an ATP/GTP-binding site, three leucine zipper domains, and a leucine-rich tandem repeat, which are structural or functional elements for interactions among proteins related to the cell cycle, and which suggest that overexpression might be oncogenic with respect to MFH.	19.16
AW401864	Hs.18720	PDCD8, programmed cell death 8 (apoptosis-inducing factor)	Mitochondrial apoptosis-inducing factor; flavoprotein inducing chromatin condensation and DNA fragmentation	19.01
AA186241	Hs.73980	zp88f03.r1 Stragene muscle 937209 Homo sapiens cDNA clone IMAGE:628253 5' similar to gb:M19309 TROPONIN T, SLOW SKELETAL MUSCLE ISOFORMS (HUMAN); mRNA sequence	Function unknown	18.82
NM_004998	Hs.82251	MYO1E, myosin IE	Highly similar to class I myosin; may bind proline-rich peptides; contains an Src homology 3 (SH3) and myosin head domain (motor domain)	18.62
AW873704	Hs.320831	C20orf72: chromosome 20 open reading frame 72	Function unknown	18.19
AW361868	Hs.49500	KUAA0746: KIAA0746 protein	Function unknown	18.05
BE174595	Hs.386	PTS, 6-pyruvoyltetrahydropterin synthase	6-Pyruvoyltetrahydropterin synthase; synthesizes tetrahydrobiopterin, activity requires sepiapterin reductase, Mg ²⁺ , and NADPH	17.28
M31669	Hs.1735	Human inhibin beta-B-subunit gene, exon 2, and complete cds	Function unknown	16.24
AK001714	Hs.95744	FLJ10852, hypothetical protein similar to ankyrin repeat-containing protein AKR1	Are involved in protein-protein interactions; has five ankyrin repeats and a DHHC-type zinc finger or NEW1 domain	16.09
AU076517	Hs.184276	AU076517 Sugano cDNA library Homo sapiens cDNA clone ColF3365 similar to 5'-end region of Homo sapiens ezrin-radixin-moesin binding phosphoprotein-50 mRNA, mRNA sequence	Function unknown	16.05

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
NM_008456	Hs.288215	STHM, stialytransferase	Low similarity to beta-galactosidase α -2,3-sialyltransferase SIAT4B; member of the sialyltransferase family	15.93
BE148235	Hs.193063	Homo sapiens cDNA FLJ14201 fis, clone NT2RP3002855	Function unknown	15.91
AV653729	Hs.8185	SORDL: sulfide dehydrogenase like (yeast)	Sulfide dehydrogenase like	15.35
AL119871	Hs.1420	FGFR3, fibroblast growth factor receptor 3 (achondroplasia, thanatophoric dwarfism)	Fibroblast growth factor receptor 3; receptor tyrosine kinase that binds acidic and basic FGF	14.62
AA393071	Hs.182579	LAP3, leucine aminopeptidase	Leucine aminopeptidase	14.60
AL048753	Hs.303649	CCL2, chemokine (C-C motif) ligand 2	Cytokine A 2; chemotactic factor for monocytes	14.37
AI868872	Hs.282804	CP, ceruloplasmin (ferroxidase)	Ceruloplasmin; ferrous oxidase, binds copper in plasma and maintains iron homeostasis	14.07
NM_004419	Hs.2128	DUSP5, dual specificity phosphatase 5	Mitogen inducible dual specificity protein phosphatase 5; dephosphorylates extracellular signal-regulated kinase	14.05
AW969587	Hs.86368	EST381684 MAGE resequences, MAGK Homo sapiens cDNA, mRNA sequence	Function unknown	13.75
AW161449	Hs.72290	WNT7A, wingless-type MMTV/Integration site family, member 7A	Very strongly similar to murine Wnt7a; may have a role in limb development and sexual dimorphism; member of the Wnt family of cell signalling proteins	13.48
BE409838	Hs.194657	CDH1, cadherin 1, type 1, E-cadherin (epithelial)	E-cadherin (uvomolulin); Ca ²⁺ -dependent glycoprotein, mediates cell-cell interactions in epithelial cells	12.92
BE540274	Hs.239	FOXM1, forkhead box M1	Cell-cycle regulated HNF-3/fork head; a transcriptional regulator	12.86
AF022375	Hs.73793	VEGF, vascular endothelial growth factor	Vascular endothelial growth factor; induces endothelial cell proliferation and vascular permeability	12.79
AW369278	Hs.23412	FLJ20160: hypothetical protein FLJ20160	Function unknown	12.73
AF147204	Hs.89414	CXCR4, chemokine (C-X-C motif), receptor 4 (fusin)	CXC chemokine receptor (fusin); G protein-coupled receptor binds CXC cytokines, mediates intracellular calcium flux	12.56
BE242818	Hs.311609	DDX39, DEAD/H (Asp-Glu-Ala-Asp/His) box polypeptide 39	Strongly similar to human DDX39E; member of the DEAD/H box ATP-dependent RNA helicase family	12.43
NM_014791	Hs.184339	MELK, maternal embryonic leucine zipper kinase	Leucine zipper kinase	12.25
U38847	Hs.151518	TARBP1, TAR (HIV) RNA binding protein 1	Binds to the HIV-1 TAR RNA regulatory element, may function alone or with HIV-1 Tat to disengage RNA polymerase II during transcriptional elongation; has a leucine zipper	12.22
AW953575	Hs.303125	EST365645 MAGE resequences, MAGC Homo sapiens cDNA, mRNA sequence	Function unknown	12.21

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
AI848085	Hs.67776	ESTs, Weakly similar to T22341 hypothetical protein F47B8.5 - <i>Caenorhabditis elegans</i> [C.elegans]	Homo sapiens, clone IMAGE:5455669, mRNA, partial cds	12.08
BE274530	Hs.273333	FLJ10986, hypothetical protein FLJ10986	Member of the FGGY carbohydrate kinase family	11.75
AB020876	Hs.21543	KIAA0869 protein	Function unknown	11.73
		Target Exon	Function unknown	11.69
H48299	Hs.26126:33	CLDN10, claudin 10	Cell adhesion, integral plasma membrane protein, tight junction.	11.67
T34530	Hs.4210	Homo sapiens cDNA FLJ13069 fis, clone NT2RP3001752	Function unknown	11.50
NM_022454	Hs.97984	SOX17, SRY (sex determining region Y)-box 17	SRY-related HMG-box transcription factor SOX17	11.42
AA737033	Hs.7165	Homo sapiens, clone IMAGE:4428577, mRNA, partial cds	Function unknown	10.79
AA433988	Hs.98502:8	MUC16, mucin 16, CA125	Mucin 16, Alias CA125 ovarian cancer antigen	10.52
H91282	Hs.286232	Homo sapiens cDNA: FLJ23190 fis, clone LNG12190	Function unknown	10.50
AW005054	Hs.47883	LOC57118: CamK1-like protein kinase	CamK1-like protein kinase; granulocyte-specific protein kinase that activates ERK/MAP kinase activity; similar to Ca(2+)-calmodulin-dependent kinase I (CamK1)	10.49
X69699	Hs.73149	PAX8, paired box gene 8	Member of the paired domain family of nuclear transcription factors; are involved in the ribosome assembly, required for normal thyroid development	10.39
AW382987	Hs.88474:42	Homo sapiens cDNA, mRNA sequence	Function unknown	10.21
AW957446	Hs.301711	Homo sapiens, clone MGC:23936 IMAGE:3638595, mRNA, complete cds	Function unknown	10.12
AA361562	Hs.178761	POH1: 26S proteasome-associated pad1 homolog	Ubiquitin-dependent protein degradation	10.01
AA834626		RAD54L, RAD54 (<i>S.cerevisiae</i>)-like	Has likely roles in mitotic and meiotic DNA recombination and repair; member of SNF2/SWI2 family of DNA-dependent ATPases	9.85
AI878927	Hs.76284	MEST, mesoderm specific transcript (mouse) homolog	Mesoderm specific protein; member of the alpha/beta hydrolase fold family	9.83
AW074266	Hs.23071	LOC85439: stonin 2	Stonin 2	9.74
NM_000947	Hs.74519	PRIM2A, primase, polypeptide 2A (58kD)	Subunit of DNA primase polypeptide 2A; part of the DNA polymerase alpha-primase complex	9.72

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
NM_006187	Hs.56009	OAS3, 2'-5'-oligoadenylate synthetase 3 (100 kD)	Member of the 2'-5'-oligoadenylate synthetase family	9.68
AW278558	Hs.81256	S100A4, S100 calcium binding protein A4 (calcium protein, calvasculin, metastasin, murine placental homolog)	Calcyclin (metastasis-associated) (S100 calcium-binding protein A4); Interacts with targets to link extracellular stimuli and cellular responses; member of the S100 family of tissue-specific calcium-binding proteins	9.66
T18997	Hs.180372	LOC139231: hypothetical protein BC016683	Function unknown	9.49
AA262284	Hs.180383	DUSP6, dual specificity phosphatase 6	Dual specificity protein phosphatase 6; selectively dephosphorylates and inactivates MAP kinase	9.48
AA220238	Hs.94986	RPP38; ribonuclease P (38kD)	Nucleus; ribonuclease P. Subunit p38 of ribonuclease P	9.41
AW505308	Hs.75812	PCK2, phosphoenolpyruvate carboxykinase 2 (mitochondrial)	Phosphoenolpyruvate carboxykinase 2; forms phosphoenolpyruvate by decarboxylation of oxaloacetate at the rate-limiting step of gluconeogenesis	9.38
AI186431	Hs.286638	PLAB; prostate differentiation factor	Macrophage inhibitory cytokine; member of a subgroup of the TGF-beta superfamily	9.12
AI095718	Hs.135015	Homo sapiens cDNA FLJ40908 fis, clone UTRU2004698, highly similar to Mus musculus mRNA for thrombospondin type 1 domain	Function unknown	9.04
W70171	Hs.75939	UMPK, uridine monophosphate kinase	The protein encoded by this gene catalyzes the phosphorylation of uridine monophosphate to uridine diphosphate. This is the first step in the production of the pyrimidine nucleoside triphosphates required for RNA and DNA synthesis. In addition, an allele of this gene may play a role in mediating nonhumoral immunity to Hemophilus influenzae type B.	8.97
AI580935	Hs.105898	Homo sapiens cDNA FLJ31553 fis, clone NT2R2001178	Function unknown	8.90
AB040914	Hs.278628	ShrmL; Shroom-related protein	Shroom-related protein	8.87
AU076611	Hs.164872	MTFSD2, methylene tetrahydrofolate dehydrogenase (NAD+ dependent), methylenetetrahydrofolate cyclohydrolase	NAD-dependent methylene tetrahydrofolate dehydrogenase-cyclohydrolase; may provide formyltetrahydrofolate for formylmethionyl tRNA synthesis; involved in initiation of mitochondrial protein synthesis	8.71
AI089660	Hs.323401	LOC84661: dpy-30-like protein	dpy-30-like protein	8.71
D13666	Hs.136348;228;Hs.80988;2	OSF-2; osteoblast specific factor 2 (fasciclin I-like)	Cell adhesion, skeletal development. Putative bone adhesion protein; similar to the insect protein fasciclin I	8.64
AI798863	Hs.67191	ESTs	Function unknown	8.52

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
U78093	Hs.15154	SRPX, sushi-repeat-containing protein, X chromosome	Putative membrane protein with short consensus repeat (sushi) domains	8.51
AI669760	Hs.188881	ESTs	Function unknown	8.37
AI375726	Hs.279918	MGC2198: hypothetical protein MGC2198	Function unknown	8.37
AW271108	Hs.133294	ESTs	Function unknown	8.30
AK001782	Hs.15093	HSPC195: hypothetical protein HSPC195	Function unknown	8.18
AF019226	Hs.8036	RAB3D, RAB3D, member RAS oncogene family	GTP-binding protein; are involved in vesicle transport; member of the RAB family of small GTPases	7.94
AW988343	Hs.24255	LOC150696: prominin-related protein	Prominin-related protein	7.90
AF111858	Hs.105039	SLC34A2, solute carrier family 34 (sodium phosphate), member 2	Sodium-dependent phosphate transporter; member of the renal type II co-transporter family	7.87
AA863360	Hs.26040	Homo sapiens, clone MGC:40051 IMAGE:5243005, mRNA, complete cds	Function unknown	7.75
NM_005764	Hs.271473	DD98: epithelial protein up-regulated in carcinoma, membrane associated protein 17	Up-regulated in malignant epithelial cells of renal cell carcinomas, and in carcinomas of colon, breast and lung	7.75
AW360901	Hs.183047	MGC4399: mitochondrial carrier protein	Mitochondrial carrier protein MGC4399	7.71
AL353944	Hs.60115	Homo sapiens mRNA; cDNA DKFZp761J1112 (from clone DKFZp761J1112)	Function unknown	7.69
H59789	Hs.42644	TXNL2, thioredoxin-like 2	Member of the thioredoxin family; has region of moderate similarity to glutaredoxin-like proteins	7.65
NM_002984	Hs.75703	CCL4, chemokine (C-C motif) ligand 4	Cytokine A4	7.64
AA642452	Hs.130881	BCL11A, B-cell CLL/lymphoma 11A (zinc finger protein)	May bind nucleic acids; contains three C2H2 type zinc finger domains	7.61
AA789081	Hs.4029	GAS41: glioma-amplified sequence-41	Similar to the transcription factors AF-9 and ENL	7.46
H13032	Hs.103378	MGC11034, hypothetical protein MGC11034	Function unknown	7.42
BE384836	Hs.3454	KIAA1821: KIAA1821 protein	KIAA1821 protein	7.40
AW067800	Hs.155223	STC2, stanniocalcin 2	Stanniocalcin 2; may regulate metal ion homeostasis and inhibits phosphate uptake	7.38
T55979	Hs.115474	RFC3, replication factor C (activator 1) 3 (38kD)	Subunit of replication factor C (activator 1) 3; activator of DNA polymerases	7.35
AJ278016	Hs.55565	ANKRD3, ankyrin repeat domain 3	Ortholog of mouse protein kinase C-associated kinase, putative gene, ankyrin like, possible dual-specificity Ser/Thr/Tyr kinase domain	7.25

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
		NM_025080: Homo sapiens hypothetical protein FLJ2316 (FLJ2316), mRNA, VERSION NM_025078.1 GI:13376631	Function unknown	7.22
AA084248	Hs.85339:64	GPR39, G protein-coupled receptor 39	GPR39, G protein-coupled receptor 39	7.15
BE620738	Hs.173125	PPIF, peptidylprolyl isomerase F (cyclophilin F)	Cyclophilin F (peptidylprolyl isomerase F); binds the immunosuppressant drug cyclosporin A	7.06
AF072873	Hs.114218	FZD6, frizzled (Drosophila) homolog 6	Frizzled-6; may function in tissue polarity, development and carcinogenesis; similar to frizzled receptor family, has seven transmembrane domains	7.04
AA852773	Hs.334838	KIAA1866 protein	KIAA1866 protein	6.99
R07566	Hs.73817	CCL3, chemokine (C-C motif) ligand 3	Macrophage inflammatory protein 1 alpha; chemokine	6.98
NM_005211	Hs.174142	CSF1R, colony stimulating factor 1 receptor, formerly McDonough feline sarcoma viral (v-fms) oncogene homolog	Macrophage colony stimulating factor tyrosine kinase receptor; involved in regulation of growth and differentiation of myeloid cells	6.79
A1752666	Hs.76689	NNMT, nicotinamide N-methyltransferase	Nicotinamide N-methyltransferase; catalyzes the N-methylation of nicotinamide and other pyridines, structurally-related drugs and xenobiotics	6.52
AF182294	Hs.241578	LOC51681: U6 snRNA-associated Sm-like protein LSM8	Member of the Sm family; core constituent of snRNP complexes	6.50
AA457211	Hs.8858	BAZ1A, bromodomain adjacent to zinc finger domain, 1A	May bind DNA and act as a chromatin-mediated transcriptional regulator; contains a bromodomain and a PHD-finger	6.48
W40262	Hs.146310	zcf902.s1 Pancreatic Islet Homo sapiens cDNA clone IMAGE:328539 3', mRNA sequence	Function unknown	6.47
AB033091	Hs.74313	KIAA1285 protein	Function unknown	6.45
AA292988	Hs.163900	ESTs, Highly similar to winged helix/forkhead transcription factor [Homo sapiens] [H.sapiens]	Function unknown	6.36
BE613269	Hs.21893	DKFZp761N0624: hypothetical protein DKFZp761N0624	Function unknown	6.35
H25836	Hs.301527	ESTs, Moderately similar to unknown [Homo sapiens] [H.sapiens]	Function unknown	6.27
AL037228	Hs.82043	NUDT5, nudix (nucleoside diphosphate linked moiety X)-type motif 5	NDP-sugar hydrolase; converts ADP-ribose to AMP or ribose 5-phosphate; contains a MutT motif	6.25
AV662037	Hs.124740	FLJ30532: hypothetical protein FLJ30532	Function unknown	6.21

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
AI674383	Hs.22891	wc38f08.x1 NC1 CGAP_F128 Homo sapiens cDNA clone IMAGE:2320959 3', mRNA sequence	Function unknown	6.20
AW342140	Hs.182545	ESTs, Weakly similar to POL2, MOUSE Retrovirus-related POL polyprotein [Contains: Reverse transcriptase ; Endonuclease] [M.musculus]	Function unknown	6.18
BE560135	Hs.5232	HSPC125, HSPC125 protein	Function unknown	6.17
BE409857	Hs.69488	HSPC132: hypothetical protein HSPC132	Moderately similar to a region of <i>S. cerevisiae</i> Yk053c-ap	6.16
AW972542	Hs.289008	LOC116150: hypothetical protein, MGC:7199	Function unknown	6.16
AI523755	Hs.59236	DKFZP434L0718: hypothetical protein DKFZp434L0718	Function unknown	6.16
NM_014056	Hs.7917	DKFZP564K247: DKFZP564K247 protein	Function unknown	6.08
AI857607	Hs.181301	CTSS, cathepsin S	Cathepsin S; lysosomal cysteine (thiol) protease that cleaves elastin	6.04
AW247529	Hs.6783	PAFAH1B3, platelet-activating factor acetylhydrolase, isoform lb, gamma subunit (28kD)	Platelet-activating factor acetylhydrolase gamma; may play a role in brain development	5.98
AK000868	Hs.5570	Homo sapiens cDNA FLJ10006 fis. clone HEMBA1000168, weakly similar to CYLICIN 1	Function unknown	5.92
AF053551	Hs.31584	MTX2, metaxin 2	Very strongly similar to murine metaxin 2 (Mm.12941); are involved in mitochondrial protein import	5.91
AI538613	Hs.298241	TMPPRSS3, Transmembrane protease, serine 3	The encoded protein contains a serine protease domain, a transmembrane domain, a LDL receptor-like domain, and a scavenger receptor cysteine-rich domain. This gene was identified as a tumor associated gene that is overexpressed in ovarian tumors.	5.86
U48508	Hs.89631	Human skeletal muscle ryanodine receptor gene (RYR1), exons 103, 104, 105, 106, and complete cds	Function unknown	5.86
T69387	Hs.76364	AIF1, allograft inflammatory factor 1	Allograft inflammatory factor 1; cytokine inducible protein associated with vascular injury	5.86
AC005954	Hs.25527	Homo sapiens chromosome 19, cosmid R28784, complete sequence	Function unknown	5.86
AB037805	Hs.88442	KJAA1384 protein	Function unknown	5.84

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
AL031427	Hs.40084	Human DNA sequence from clone 167A19 on chromosome 1p32.1-33. Contains three genes for novel proteins, the DIO1 gene for type I iodothyronine deiodinase (EC 3.8.1.4, TXD1, ITD1) and an HNRNP A3 (Heterogenous Nuclear Ribonucleoprotein A3, FBRNP) pseudogene.	Function unknown	5.83
AA340864 X89984 AI355781	Hs.278562 Hs.211563 Hs.242463	CLDN7, claudin 7 BCL7A, B-cell CLL/lymphoma 7A q84a11.x1 NCL CGAP_Co14 Homo sapiens cDNA clone IMAGE:1662808.3 similar to gb:X74929 KERATIN, TYPE II CYTOSKELETAL 8 (HUMAN); mRNA sequence	Similar to murine Cldn7; are an integral membrane protein Similar to the actin-binding protein caldesmon; serine-rich Function unknown	5.76 5.74 5.73
AA376409	Hs.10862	Homo sapiens cDNA: FLJ23313 fis, clone HEP11919	Function unknown	5.71
AA310162 AW015534	Hs.169248 Hs.217493	HCS: cytochrome c ANXA2, annexin A2	Somatic cytochrome c (heart cytochrome c) Annexin II (lipocortin-2); enhances osteoclast formation and bone resorption; member of the annexin protein family	5.67 5.64
AA326108	Hs.53631.82	BHLHB3; basic helix-loop-helix domain containing, class B, 3	Basic helix-loop-helix (bHLH) transcription factors (e.g., DEC1, also called BHLHB2; 604256) are related to Drosophila hairy/enhancer of split proteins. They are involved in the control of proliferation and development during differentiation, particularly in neurons.	5.64
AA120865	Hs.23136	ESTs, Highly similar to THYA_HUMAN Prothymosin alpha [H.sapiens]	Function unknown	5.62
AK000517 Z38842 AA831552	Hs.6844 Hs.57548 Hs.268016	NALP2; NALP2 protein H.sapiens (xs85) mRNA, 209bp Homo sapiens cDNA: FLJ21243 fis, clone COL01164	Protein with low similarity to murine Op1 Function unknown	5.64 5.53 5.50
AL137578	Hs.27607	Homo sapiens mRNA; cDNA DKFZp564N2464 (from clone DKFZp564N2464)	Function unknown	5.50
AA316181	Hs.61635	STEAP, six transmembrane epithelial antigen of the prostate	Six transmembrane epithelial antigen of the prostate; prostate-specific cell-surface antigen	5.46

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
X03635	Hs.1657	ESR1, estrogen receptor 1	Estrogen receptor; nuclear receptor transcription factor activated by ligand-binding. Involved in hormone-mediated inhibition of gene expression	5.42
AU557280	Hs.184270	PTZ1_15_G11.r tumor2 Homo sapiens cDNA 3', mRNA sequence	Function unknown	5.41
AY248508	Hs.279727	Homo sapiens cDNA FLJ14035 fis, clone HEMBA1004838	Function unknown	5.40
N90866	Hs.276770	CDW52, CDW52 antigen (CAMPATH-1 antigen)	CAMPATH-1 antigen; GPI-anchored protein	5.39
U83115	Hs.161002	AIM1, absent in melanoma 1	Member of the beta gamma-crystallin superfamily of proteins; interactions with the cytoskeleton	5.35
AB007860	Hs.12802	DDEF2, development and differentiation enhancing factor 2	GTPase-activating protein; interacts with members of the Arf and Src family	5.35
Z46223	Hs.176663	H.sapiens DNA for Immunoglobulin G Fc receptor IIIB	Immunoglobulin G Fc receptor	5.31
BE264974	Hs.6566	TRIP13; thyroid hormone receptor Interactor 13	Interacts with ligand binding domain of thyroid hormone receptor and with human papillomavirus type 18 (HPV16) E1	5.30
AA194422	Hs.22594	MYO6, myosin VI	Motor; hearing, myosin ATPase, structural protein. Class 6 myosin; motor protein; very strongly similar to murine Myo6	5.27
AF134157	Hs.169487	MAFB, v-maf musculoaponeurotic fibrosarcoma oncogene homolog B (avian)	Very strongly similar to murine Krm1; may function as a basic domain-leucine zipper transcription factor	5.25
AA232119	Hs.16085	SH120; putative G-protein coupled receptor	putative G-protein coupled receptor	5.25
W58353	Hs.285123	OSBPL10, oxysterol binding protein-like 10	Member of the oxysterol-binding protein (OSBP) family, may bind oxygenated derivatives of cholesterol	5.21
AW167128	Hs.231934	ESTs, Weakly similar to A57717 transcription factor EC2 - human [H.sapiens]	Function unknown	5.19
U70370	Hs.84136	PITX1, paired-like homeodomain transcription factor 1	Member of the homeodomain family of DNA binding proteins; may regulate gene expression and control cell differentiation	5.18
N55669	Hs.333823	MRPL13, mitochondrial ribosomal protein L13	Protein of the large 60S ribosomal subunit	5.17
BE298446	Hs.305880	BCL2L1, BCL2-like 1	BCL2-related protein; alternative form bcl-xlong inhibits apoptosis and bcl-xshort induces apoptosis	5.17
AW136551	Hs.181245	Homo sapiens cDNA FLJ12532 fis, clone NT2RM4000200	Function unknown	5.15
AW250380	Hs.109059	HGS, hepatocyte growth factor-regulated tyrosine kinase substrate	Zinc-finger protein; interacts with STAM, undergoes tyrosine phosphorylation in response to IL2, CSF2, or HGF	5.13

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
AW002565	Hs.124660	Homo sapiens cDNA: FLJ21763 fls. clone COLF6967	Function unknown	5.13
AI697274	Hs.105435	GMDS, GDP-mannose 4,6-dehydratase	GDP-mannose-4,6-dehydratase; epimerase converts GDP-mannose to GDP-mannose-4-keto-6-D-deoxymannose, plays a role in the synthesis of fucosylated oligosaccharides	5.11
NM_003878	Hs.78619	GGH, gamma-glutamyl hydrolase (conjugase, foxylypolygamma-glutamyl hydrolase)	Gamma-glutamyl hydrolase; has greater exopeptidase activity on methotrexate pentaglutamate than on diglutamate	5.11
AF052112	Hs.12540	LYPLA1, lysophospholipase I	Lysophospholipid-specific lysophospholipase 1; hydrolyzes lysophosphatidyl choline	5.09
AV654694	Hs.82316	IFI44, interferon-induced protein 44	Member of the family of Interferon-alpha/beta inducible proteins; may mediate the antiviral action of Interferon	5.09
R24601		Homo sapiens adenylosuccinate synthetase isozyme (ADSS) mRNA, complete cds	Adenylosuccinate synthetase	5.07
BE019020	Hs.85838	Homo sapiens cDNA clone IMAGE:2983945 5' similar to TR:O15427 O15427 MONOCARBOXYLATE TRANSPORTER. 1; mRNA sequence	Function unknown	5.04
AW163799	Hs.198365	BPGM, 2,3-bisphosphoglycerate mutase	2,3-bisphosphoglycerate mutase; has synthase, mutase, and phosphatase activities, controls 2,3-diphosphoglycerate metabolism, which is an effector for haemoglobin	5.04
AA278921	Hs.1908	PRG1, proteoglycan 1, secretory granule	Secretory granule proteoglycan 1	5.02
NM_003726	Hs.19126	SCAP1, src family associated phosphoprotein 1	Src kinase-associated phosphoprotein; acts as an adaptor protein; contains a pleckstrin homology domain and an SH3 domain	5.02
AA281167	Hs.111911	ESTs, Weakly similar to T08291 extensin homolog T08280 - Arabidopsis thaliana [A.thaliana]	Function unknown	5.02
		C9000306*gi12737280 ref XP_006682.2 keratin 18 [Homo sapiens]] 6633	Function unknown	5.01
AF098158	Hs.9329	C20orf1, chromosome 20 open reading frame 1	Proliferation-associated nuclear protein; associates with the spindle pole and mitotic spindle during mitosis	5.00

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
AA101043	Hs.151254:19	KLK7, kallikrein 7 (chymotryptic; stratum corneum)	Epidermal differentiation. Stratum corneum chymotryptic enzyme; serine protease. Growing evidence suggests that many kallikreins are implicated in carcinogenesis and some have potential as novel cancer and other disease biomarkers. Thought to be involved in the proteolysis of intercellular cohesive structures preceding desquamation, which is the shedding of the outermost layer of the epidermis. Function unknown	4.87
AF017986	Hs.31386:185	Homo sapiens secreted apoptosis related protein 1 (SARP1) mRNA, partial cds.		4.12
AW980564	Hs.3337:137	TM4SF1; transmembrane 4 superfamily member 1	Pathogenesis, plasma membrane, cell proliferation, N-linked glycosylation, integral membrane protein, integral plasma membrane protein, Ig antigen; member of the transmembrane 4 superfamily (TM4SF). The proteins mediate signal transduction events that play a role in the regulation of cell development, activation, growth and motility. This encoded protein is a cell surface antigen and is highly expressed in different carcinomas.	3.62
W29092	Hs.7678:40	CRABP1 Cellular retinoic acid binding protein 1	Cytoplasm, retinoid binding, signal transduction, developmental processes. Cellular retinoic acid-binding protein 1; are involved in delivering retinoic acid to the nucleus, assumed to play an important role in retinoic acid-mediated differentiation and proliferation processes. Function unknown	3.34
H93368	Hs.7587:84	Homo sapiens cDNA: FLJ21962 fls, clone HEP05584		3.29
D49441	Hs.155981:53	MSLN, mesothelin	Cell adhesion, cell surface antigen, membrane. Pre-pro-megakaryocyte potentiating factor. An antibody that reacts with ovarian cancers and mesotheliomas was used to isolate a cell surface antigen named mesothelin. Although the function of mesothelin is unknown, it may play a role in cellular adhesion and is present on mesothelium, mesotheliomas, and ovarian cancers. Region of high similarity to tyrosine-phosphorylated protein DOK1	3.14
AA214228	Hs.127751:21,Hs.78006:5	C20orf180: chromosome 20 open reading frame 180		2.99
M31126	Hs.272620:1	PSG9: pregnancy specific beta-1-glycoprotein 9	Pregnancy, extracellular, plasma glycoprotein. Member of the pregnancy-specific glycoprotein (PSG) and CEA families.	2.82
U62801	Hs.79361:65	KLK6, kallikrein 6 (neurosin, zyme)	Serine type peptidase, pathogenesis. Neurosin (protease M, zyme); a serine protease that cleaves amyloid precursor protein (APP). Growing evidence suggests that many kallikreins are implicated in carcinogenesis and some have potential as novel cancer and other disease biomarkers. Function unknown	2.77
AK001636	Hs.285803:6	Homo sapiens cDNA FLJ12852 fls, clone NT2RP2003445		2.73

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
NM_014767	Hs.74583:140	KIAA0275: KIAA0275 gene product	Function unknown	2.72
NM_000699	Hs.75733:129,Hs.278398:100,Hs.274376:1	AMY2A: amylase, alpha 2A; pancreatic	Alpha-amylase, extracellular space, carbohydrate metabolism. Pancreatic alpha-amylase 2A (1,4-alpha-D-glucan glucanohydrolase); cleaves internal α -1,4 bonds between glucose monomers to digest starch.	2.71
AA430348	Hs.288837:40	Homo sapiens cDNA FLJ12927 fis, clone NT2RP2004743	Function unknown	2.89
X51630	Hs.1145:22,Hs.296851:1	WT1, Wilms tumor 1	Nucleus, transcription factor, transcription regulation. 4 Zn finger domains. Functions in kidney and gonad proliferation and differentiation. Mutations in this gene are associated with the development of Wilms tumors in the kidney or with abnormalities of the genitourinary tract.	2.58
BE393948	Hs.50915:17	KLK5, kallikrein 5	Serine type peptidase, epidermal differentiation, extracellular space. Stratum corneum typtic enzyme (kallikrein-like protein); may function in epidermal stratum corneum desquamation and turnover. Expression in prostate cancer negatively correlated with cancer aggressiveness (Yousef 2002)	2.34
NM_002776	Hs.68423:40	KLK10, kallikrein 10	Putative serine protease. Expressed in normal breast tissue and benign lesions, with loss of expression during tumor progression (Dhar 2001). SNPs associated with prostate, breast, testicular, and ovarian cancers (Bharaj 2002).	2.24
NM_000954	Hs.8272:294	PTGDS: prostaglandin D2 synthase (21kD, brain)	Membrane, prostaglandin-D synthase. Glutathione-independent prostaglandin D2 synthase; membrane associated, catalyzes synthesis of prostaglandin D; member of the lipocalin family of transporters.	2.15
AB029000	Hs.70823:109,Hs.297870:48	KIAA1077: sulfatase FP	Function unknown	2.04
AL044315	Hs.173094:70	KIAA1750; KIAA1750 protein	Function unknown	0.95
AA334592	Hs.79914:337	LUM: lumican	Vision, proteoglycan, extracellular matrix, cartilage condensation, extracellular matrix glycoprotein. Member of the specialized collagens and SLRP family	0.93
S79895	Hs.83942:248	CTSK: cathepsin K (pseudosclerosis)	Lysosome, cathepsin K, cysteine-type peptidase, proteolysis and peptidolysis. Cathepsin K (cathepsin O), a cysteine (thiol) protease; involved in bone remodeling and reabsorption	0.91
AI091195	Hs.65029:120	Homo sapiens cDNA clone IMAGE:1566910 3', mRNA sequence	Function unknown	0.91

Accession number	UniGene Mapping	Gene symbol and title	Putative Function	Ratio
AF028692; NM_003014	Hs.105700:33; Hs.278611:3	SFRP4; secreted frizzled-related protein 4	Member of the SFRP family that contains a cysteine-rich domain homologous to the putative Wnt-binding site of Frizzled proteins. SFRPs act as soluble modulators of Wnt signaling. The expression of SFRP4 in ventricular myocardium correlates with apoptosis related gene expression. Function unknown	0.73
A1683243	Hs.97258:15	ESTs, Moderately similar to S29539 ribosomal protein L13a, cytosolic	Function unknown	-2.96
A1287700	Hs.111128:7	Homo sapiens, clone IMAGE:4106329, mRNA	Function unknown	-5.71
AA291377	Hs.50831:23	Homo sapiens Ly-6 antigen/UPA receptor-like domain-containing protein mRNA, complete cds	Function unknown	-6.78
A1420213	Hs.149722:3	cDNA clone IMAGE:2094208 3', mRNA sequence	Function unknown	-8.52
AJ245671	Hs.12844:73	EGFL6, EGF-like-domain; multiple 6	Cell cycle, oncogenesis, Integrin ligand, extracellular space. Member of the epidermal growth factor (EGF) repeat superfamily; contains an EGF-like-domain. Expressed early during development, and its expression has been detected in lung and meningioma tumors.	-9.44
AB018305	Hs.5378:149	SPON1, spondin 1, (k-spondin) extracellular matrix protein	Extracellular matrix protein. Very strongly similar to rat F-spondin (Rn.7546); may have a role in the growth and guidance of axons.	-12.55
AW872527	Hs.59761:19	ESTs; Weakly similar to DAP1_HUMAN DEATH-ASSOCIATED PROTEIN 1	Function unknown	-14.17
AF129755	Hs.117772:9; Hs.88474:1	Homo sapiens prostaglandin endoperoxide H synthase-1 mRNA, partial 3' untranslated region.	Function unknown	-21.34
A1023789	Hs.163242:5	Homo sapiens cDNA clone IMAGE:1655725 3' similar to contains MER20.12 MER20 repetitive element.; mRNA sequence	Function unknown	-41.34

Table 3
Preferred diagnostic and prognostic markers for detecting ovarian cancer or a recurrence thereof
or survival of a subject suffering from ovarian cancer

A. DOWN-REGULATED GENES					
Accession Number	Unigene Mapping	Gene Name	Function	SEQ ID NO:	Chromosome Location P value
AI631024; NM_005460	Hs.24948:32; Hs.300445:4	SNCAIP, alpha synuclein, alpha interacting protein (synphilin)	Cytoplasm, pathogenesis, protein binding. Synphilin-1; promotes formation of cytosolic inclusions in neurons (SNCAIP). Synuclein alpha interacting protein contains several protein-protein interaction domains and interacts with alpha synuclein in neurons. Mutations of SNCAIP have been linked to Parkinson disease.	SEQ ID NO: 1 (DNA) SEQ ID NO: 2 (PRT)	5q23.2 0
NM_002387	Hs.1345:5	MCC, mutated in colorectal cancers	Receptor, signal transduction, tumor suppressor. Similar to the G protein-coupled m3 muscarinic acetylcholine receptor. MCC is a candidate for the putative colorectal tumor suppressor gene. The MCC gene product are involved in early stages of colorectal neoplasia in both sporadic and familial tumors.	SEQ ID NO: 3 (DNA) SEQ ID NO: 4 (PRT)	5q22.2 0
AI420582; NM_022117	Hs.138164:23	SE20-4, cutaneous T-cell lymphoma-associated tumor antigen se20-4	Cutaneous T-cell lymphoma-associated tumor antigen se20-4se20-4; differentially expressed nuclear TGF-beta1 target protein (DENTT); also known as CDA1	SEQ ID NO: 5 (DNA) SEQ ID NO: 6 (PRT)	unmapped 0

Table 3 continued

Accession Number	Unigene Mapping	Gene Name	Function	SEQ ID NO:	Chromosome Location	P value
B. UP-REGULATED GENES						
BC006428; NM_016463	Hs.15093:210;Hs.290304:1	HSPC195, hypothetical protein HSPC195 FLJ20171.	Homo sapiens cDNA FLJ10920 fis, clone OVARC1000384-resourcer.	SEQ ID NO: 7 (DNA) SEQ ID NO: 8 (PRT)	5q31.2	0
NM_017697	Hs.24743:94	hypothetical protein FLJ20171	contains 3 RNA recognition motifs	SEQ ID NO: 9 (DNA) SEQ ID NO: 10 (PRT)	8q22.1	0
AW630088; NM_001306	Hs.76550:164	MAL2	Mal2 T-cell differentiation protein; found thru interaction with TPD52 which is overexpressed in breast cancer; 4 TM are involved in vesicle transport	SEQ ID NO: 11 (DNA) SEQ ID NO: 12 (PRT)	8q24.12	0
NM_015238	Hs.21543:36	KIAA0869, KIAA0869 protein; KIBRA	Function unknown	SEQ ID NO: 13 (DNA) SEQ ID NO: 14 (PRT)	5q34	0.0002
AA284879	Hs.25640:264;Hs.5372:2	CLDN3, claudin 3	Integral plasma membrane protein, pathogenesis, tight junction, transmembrane receptor. Member of the claudin family of integral membrane proteins; receptor for Clostridium perfringens enterotoxin;	SEQ ID NO: 15 (DNA) SEQ ID NO: 16 (PRT)	7q11.23	0.0004
NM_022454	Hs.97984:22	SOX17, SRY (sex determining region Y)-box 17	Likely ortholog of mouse SRY-box containing gene 17; alias SOX17	SEQ ID NO: 17 (DNA) SEQ ID NO: 18 (PRT)	8q11.23	0.0005
NM_005682	Hs.6527:201	GPR56, G protein-coupled receptor 56	cell adhesion, cell-cell signalling, G-protein linked receptor, integral plasma membrane protein, G-protein linked receptor protein signalling pathway. Member of the G protein-coupled receptor family; similar to secretin and calcitonin receptors. 7 transmembrane domains, a mucin-like domain and cysteine box in the N-terminal region. Expressed in range of tissues, highest levels in thyroid, selectively within the monolayer of cuboidal epithelial cells of the smaller, more actively secreting follicles of human thyroid. Differentially expressed in melanoma cell lines with different metastatic potential (Zendman et al 1999).	SEQ ID NO: 19 (DNA) SEQ ID NO: 20 (PRT)	16q13	0.0012
NM_001307	Hs.278562:101	CLDN7, claudin 7	Integral membrane protein, tight junction. Similar to murine Cldn7;	SEQ ID NO: 21 (DNA) SEQ ID NO: 22 (PRT)	17p13.1	0.0016

NM_014736	Hs.81892:95	KIAA0101 gene product	function unknown; no significant hits with Superfamily	SEQ ID NO: 23 (DNA) SEQ ID NO: 24 (PRT)	15q31	0.0025
BE184455; NM_003064	Hs.251754:128,H s.245742:1	SLPI, secretory leukocyte protease inhibitor (antileukoproteina se)	Plasma protein, proteinase inhibitor. Secreted inhibitor which protects epithelial tissues from serine proteases. Found in various secretions including seminal plasma, cervical mucus, and bronchial secretions, has affinity for trypsin, leukocyte elastase, and cathepsin G. Its inhibitory effect contributes to the immune response by protecting epithelial surfaces from attack by endogenous proteolytic enzymes; the protein is also thought to have broad-spectrum anti-biotic activity.	SEQ ID NO: 25 (DNA) SEQ ID NO: 26 (PRT)	20q13.12	0.0034
NM_013994	Hs.75562:147	DDR1, discoidin domain receptor family, member 1	Cell adhesion, Integral plasma membrane protein, transmembrane receptor, protein tyrosine kinase. Epithelial-specific receptor protein tyrosine kinase; are involved in cell adhesion; has putative discoidin motifs in extracellular domain. DDR1 (CD167a) is a RTK that is widely expressed in normal and transformed epithelial cells and is activated by various types of collagen.	SEQ ID NO: 27 (DNA) SEQ ID NO: 28 (PRT)	6p21.33	0.0055
NM_001067	Hs.156346:184,H s.270810:2	TOP2A, topoisomerase (DNA) II alpha (170kD)	DNA binding, DNA topoisomerase (ATP-hydrolyzing), nucleus. DNA topoisomerase II alpha; may relax DNA torsion upon replication or transcription. Involved in processes such as chromosome condensation, chromatid separation, and the relief of torsional stress that occurs during DNA transcription and replication. Catalyzes the transient breaking and rejoining of two strands of duplex DNA. The gene encoding this enzyme functions as the target for several anticancer agents and a variety of mutations in this gene have been associated with the development of drug resistance. Reduced activity of this enzyme may also play a role in ataxia-telangiectasia.	SEQ ID NO: 29 (DNA) SEQ ID NO: 30 (PRT)	17q21.2	0.006

BE386983; NM_138410	Hs.343214	CKLFSF7; chemokine-like factor super family 7	chemokine-like factor gene superfamily; transmb 4 superfamily	SEQ ID NO: 31 (DNA) SEQ ID NO: 32 (PRT)	3p23	0.0131
AF098158; NM_012112	Hs.9329:152	C20orf1, chromosome 20 open reading frame 1	ATP binding, GTP binding, cell proliferation, mitosis, nucleus spindle. Proliferation-associated nuclear protein; associates with the spindle pole and mitotic spindle during mitosis	SEQ ID NO: 33 (DNA) SEQ ID NO: 34 (PRT)		0.0183
NM_001769	Hs.1244:227,Hs.2 30559:1,Hs.2420 20:1	CD9: CD9 antigen (p24)	Plasma membrane, integral plasma membrane protein. Member of the transmembrane 4 superfamily (TM4SF); may mediate platelet activation and aggregation. Cell surface glycoprotein that is known to complex with integrins and other transmembrane 4 superfamily proteins.	SEQ ID NO: 35 (DNA) SEQ ID NO: 36 (PRT)	12p13.31	0.0006
NM_020859	Hs.278628:52	ShrmL, Shroom- related protein (KJAA1481 protein)	Amloride-sensitive sodium channel (weakly similar to Mus musculus PDZ domain actin binding protein)	SEQ ID NO: 37 (DNA) SEQ ID NO: 38 (PRT)		0.0074
NM_004433	Hs.168096:170	ELF3, E74-like factor 3 (ets domain transcription factor, epithelial- specific)	Embryogenesis and morphogenesis, transcription co- activator, transcription factor, transcription from Pol II promoter. ETS domain transcriptional activator; activates expression of epithelial cell specific genes.	SEQ ID NO: 39 (DNA) SEQ ID NO: 40 (PRT)	1q32.1	0.0004
AI791905; NM_019027 X69699; NM_013952	Hs.95549:147,Hs. 229556:1 Hs.73148:72,Hs.2 13008:1	FLJ20273, RNA- binding protein PAX8, paired box gene 8	Contains four RNA recognition motifs (RRM, RBD, or RNP) Histogenesis and organogenesis, embryogenesis and morphogenesis, thyroid-stimulating hormone receptor, transcription factor. Member of the paired domain family of nuclear transcription factors; are involved in the ribosome assembly, required for normal thyroid development. PAX genes play critical roles during fetal development and cancer growth.	SEQ ID NO: 41 (DNA) SEQ ID NO: 42 (PRT) SEQ ID NO: 43 (DNA) SEQ ID NO: 44 (PRT)	2q13	0.0007 0.0009
AI301558	Hs.280801:35, Hs.356228	EST	Function unknown	SEQ ID NO: 45 (DNA)		0.0044
NM_018000	Hs.79741:18	FLJ10116, hypothetical protein FLJ10118	Function unknown	SEQ ID NO: 46 (DNA) SEQ ID NO: 47 (PRT)	2q35	0.0051
NM_144724	Hs.124740:18	hypothetical protein FLJ30532	59% identity to human Zinc finger protein 91	SEQ ID NO: 48 (DNA) SEQ ID NO: 49 (PRT)	5q13.12	0.0051

AF111856; NM_006424	Hs.105039:48	SLC34A2, solute carrier family 34 (sodium phosphate), member 2 (sodium phosphate), member 2	SLC34A2: solute carrier family 34 (sodium phosphate), member 2; contains 8 predicted TMs and a cysteine-rich N-terminal region. Type 2 sodium-dependent phosphate transporter, member of the renal type II co-transporter family.	SEQ ID NO: 50 (DNA) SEQ ID NO: 51 (PRT)	4p15.2	0.0121
AW959311	Hs.87019:8; Hs.172012	EST DKFZp434J037	probable serine/threonine protein kinase; KIAA0537	SEQ ID NO: 52 (DNA)	1q32.1	0.0251
AF111713	Hs.286218:64	JAM1, junctional adhesion molecule	Cell motility, inflammatory response, intercellular junction. Role in the regulation of tight junction assembly in epithelia. Ligand of JAM is required for reovirus-induced activation of NF-kappa-B and apoptosis. Role in lymphocyte homing.	SEQ ID NO: 53 (DNA) SEQ ID NO: 54 (PRT)		0.0261
AU076611; NM_006636	Hs.154672:123	MTHFD2, methylene tetrahydrofolate dehydrogenase (NAD+ dependent); methenyltetrahydrofolate cyclohydrolase	Electron transporter, methenyltetrahydrofolate cyclohydrolase, mitochondrial. encodes a nuclear-encoded mitochondrial bifunctional enzyme with methenyltetrahydrofolate dehydrogenase and methenyltetrahydrofolate cyclohydrolase activities. may provide formyltetrahydrofolate for formylmethionyl tRNA synthesis; involved in initiation of mitochondrial protein synthesis.	SEQ ID NO: 55 (DNA) SEQ ID NO: 56 (PRT)	2p13.1	0.0342

Table 3 continued

Accession Number	Unigene Mapping	Gene Name	Function	SEQ ID NO:	Chromosome Location	P value
C. UP-REGULATED GENES IN MUCINOUS OVARIAN CANCER ONLY						
AA584890; NM_006149	Hs.5302:132	LGALS4, lectin, galactoside-binding, soluble, 4 (galectin 4)	Lectin, cytosol, cell adhesion, plasma membrane. Binds to beta galactoside, involved in cell adhesion, cell growth regulation, inflammation, immunomodulation, apoptosis and metastasis; member of a family of lectins. LGALS4 is an S-type lectin that is strongly underexpressed in colorectal cancer.	SEQ ID NO: 57 (DNA) SEQ ID NO: 58 (PRT)		0.0001
	Hs.89436:50	CDH17, cadherin 17, LI cadherin (liver-intestine)	Cell adhesion, integral plasma membrane protein, membrane fraction, small molecule transport, transporter. Member of the cadherin family of calcium-dependent glycoproteins; facilitates uptake of peptide-based drugs, may mediate cell-cell interactions. Component of the gastrointestinal tract and pancreatic ducts, intestinal proton-dependent peptide transporter in the first step in oral absorption of many medically important peptide-based drugs.	SEQ ID NO: 59 (DNA) SEQ ID NO: 60 (PRT)	19q13.2	0.0172
NM_005588	Hs.179704	MEP1A, meprin A alpha, PABA peptide hydrolase	metalloprotease located apically and secreted by epithelial cells in normal colon; degrades broad range of ECM components in vitro; proposed role in tumour progression by facilitating migration, intravasation and metastasis	SEQ ID NO: 61 (DNA) SEQ ID NO: 62 (PRT)	8q22.1	0.01
					6p12	

Table 3 continued

Accession Number	Unigene Mapping	Gene Name	Function	SEQ ID NO:	Chromosome Location	P value
D. PROGNOSTIC MARKERS FOR SURVIVAL OR RECURRENCE						
NM_015092	Hs.278428	DD5; EDD	Homo sapiens progesterin induced protein (DD5), mRNA. EDD; Soluble fraction; cell proliferation; ubiquitin-protein ligase, ubiquitin conjugating enzyme, ubiquitin-dependent protein degradation. Member of the HECT family of proteins; may function as an E3 ubiquitin-protein ligase. This gene is localized to chromosome 8q22, a locus disrupted in a variety of cancers. This gene potentially has a role in regulation of cell proliferation or differentiation.	SEQ ID NO: 63 (DNA) SEQ ID NO: 64 (PRT)		0.00
BE465867; NM_014992	Hs.197751:66	DAAM1	dishevelled associated activator of morphogenesis 1 The protein encoded by this gene contains FH domains and belongs to a novel FH protein subfamily implicated in cell polarity, thought to function as a scaffolding protein.	SEQ ID NO: 65 (DNA) SEQ ID NO: 66 (PRT)	8q22.3	0.04
AA381553; NM_002122	Hs.198253:21	HLA1QA	major histocompatibility complex, class II, DQ alpha 1 Pathogenesis, class II major histocompatibility complex antigen. Alpha 1 chain of HLA-DQ1 class II molecule (la antigen); complex binds peptides and presents them to CD4+ T lymphocytes Proteome	SEQ ID NO: 67 (DNA) SEQ ID NO: 68 (PRT)	14q23.1	0.00
AF026692; NM_003014	Hs.105700:83,Hs.278611:3	SFRP4; secreted frizzled-related protein 4	Member of the SFRP family that contains a cysteine-rich domain homologous to the putative Wnt-binding site of Frizzled proteins. SFRPs act as soluble modulators of Wnt signalling. The expression of SFRP4 in ventricular myocardium correlates with apoptosis related gene expression.	SEQ ID NO: 69 (DNA) SEQ ID NO: 70 (PRT)	6p21.3 7p14	0.73
AW015534; NM_004039	Hs.217493	ANXA2, annexin A2	Annexin II (lipocortin-2); enhances osteoclast formation and bone resorption; member of the annexin protein family	SEQ ID NO: 71 (DNA) SEQ ID NO: 72 (PRT)	15q21-22	0.00
BE24669; NM_003955 AI677897; NM_014059	Hs.345728 Hs.76640	SOC33 RGC32	STAT induced STAT-inhibitor 3; suppressor of cytokine signalling 3; suppression of IL-6 mediated signalling RGC32, hypothetical protein, unknown function	SEQ ID NO: 73 (DNA) SEQ ID NO: 74 (PRT) SEQ ID NO: 75 (DNA) SEQ ID NO: 76 (PRT)	17q25.3 13q13.3	0.02 0.04

AA829286; NM_000331	Hs.332053	SAA1, serum amyloid A1 FLJ10134, hypothetical protein	Serum amyloid A1; high density lipoprotein; role in cholesterol metabolism; inflammatory response	SEQ ID NO: 77 (DNA) SEQ ID NO: 78 (PRT)	11p15.1	0.04
AA243489; NM_018004	Hs.104800	GJB2, gap junction protein beta2; connexin 26	Unknown	SEQ ID NO: 79 (DNA) SEQ ID NO: 80 (PRT)	3q12.3	0.01
M86849; NM_004004	Hs.323733	NOV1; Nephroblastoma overexpressed gene	Cellular gap junctions; mutations cause some forms of deafness	SEQ ID NO: 81 (DNA) SEQ ID NO: 82 (PRT)	13q11-12	0.00
NM_002514	Hs.235935		Role in cell adhesion and migration in endothelial cells; promotes cell survival	SEQ ID NO: 83 (DNA) SEQ ID NO: 84 (PRT)	8q24.1	0.01

Table 4

Correlation of expression between normal ovarian surface epithelium (OSE), non-invasive tumors (borderline, BL) and ovarian cancer (CA) as determined by ANOVA

	CA125	MUC-1	E-cadherin	CLDN3	Ep-CAM	SOX17
OSE vs IC	<0.0001	<0.0001	0.7251	0.6132	0.1573	0.0854
OSE vs. BL	0.1765	<0.0001	0.0307	0.3633	0.0005	0.2287
OSE vs. CA	0.5443	<0.0001	0.1687	0.0008	<0.0001	0.6900
IC vs. BL	<0.0001	<0.0001	0.1116	0.7849	0.0913	0.2530
IC vs. CA	<0.0001	0.2707	0.4147	0.0071	0.0002	0.0544
BL vs. CA	0.0001	<0.0001	0.0615	<0.0001	0.0011	0.0152

5

Table 5

Correlation of gene expression with patient outcome (univariate analysis ie., expression alone without the influence of covariates)

Univariate analysis for clinicopathological variables and CLDN3, Ep-CAM, SOX17, CA125, MUC1 and E-cadherin immunoreactivity with survival and relapse in 156 patients with epithelial ovarian cancer

Variable	Disease Specific Survival		Relapse Free Survival	
	Univariate Hazards ratio (95% CI)	p-value	Univariate Hazards ratio (95% CI)	p-value
Pathological tumor stage				
Stage 1 - 3b vs. 3c - 4b	5.89 (3.214-10.79)	<0.0001	7.37 (3.26-16.63)	<0.0001
Tumor grade				
BL and G1 vs. G2 and G3	5.508 (2.745-11.052)	<0.0001	7.02 (2.76-17.82)	<0.0001
Age				
<50 vs. ≥50	0.533 (0.288-0.988)	0.0458	0.62 (0.29-1.33)	0.2221
Residual Disease				
RD <1cm vs. ≥1cm	4.192 (2.671-6.580)	<0.0001	4.17 (2.30-7.55)	<0.0001
CA125 level at diagnosis				
CA125 <500 vs. >500 U/ml	1.843 (1.102-3.080)	0.0197	2.292 (1.19-4.40)	0.0128
Performance Status				
PS <1 vs. ≥1	0.270 (0.133-0.549)	0.0003	0.53 (0.16-1.74)	0.2965
CLDN3 expression				
Membranous Score 0 vs. >0	2.794 (1.012-7.718)	0.0474	2.521 (0.908-6.998)	0.0758
Membranous Score <1 vs. ≥1	1.309 (0.763-2.246)	0.3285	1.952 (1.103-3.457)	0.0217
Ep-CAM expression				
Membranous Score <1 vs. ≥1	1.460 (0.809-2.634)	0.2093	2.041 (0.997-4.177)	0.0509
Membranous Score <2 vs. ≥2	1.041 (0.634-1.711)	0.873	1.449 (0.845-2.487)	0.1779
SOX17 expression				
Nuclear membranous Score 0 vs. >0	0.839 (0.514-1.368)	0.481	1.311 (0.728-2.358)	0.3667
Nuclear membranous Score <1 vs. ≥1	1.407 (0.615-3.218)	0.4183	1.037 (0.380-2.829)	0.9437
CA125 expression				
Membranous apical Score 0 vs. >0	2.581 (1.393-4.781)	0.0026	2.725 (1.218-6.093)	0.0146
Membranous apical Score <1 vs. ≥1	1.637 (1.045-2.564)	0.0313	1.298 (0.731-2.307)	0.3737
MUC1 expression				
Membranous apical Score 0 vs. >0	2.479 (0.343-17.898)	0.368	NA	
Membranous apical Score <1 vs. ≥1	3.745 (1.176-11.926)	0.0254	6.432 (1.562-26.483)	0.0099
Membranous apical Score <2 vs. ≥2	1.814 (0.898-3.664)	0.0969	3.893 (1.552-9.766)	0.0038
E-cadherin expression				
Membranous Score 0 vs. >0	0.806 (0.493-1.318)	0.3892	0.837 (0.477-1.467)	0.5341
Membranous Score <1 vs. ≥1	1.331 (0.532-3.333)	0.5411	0.847 (0.263-2.731)	0.7814
Membranous Score <2 vs. ≥2	0.593 (0.082-4.284)	0.6041	0.913 (0.125-6.646)	0.9284

Table 6
Correlation of gene expression with patient outcome (multivariate analysis ie looking at expression incorporating the influence of covariates)

5

Multivariate analysis for univariate significant clinicopathological variables and CLDN3, Ep-CAM, SOX17, CA125, MUC1 and E-cadherin immunoreactivity with survival and relapse in 156 patients with epithelial ovarian cancer

Variable	Disease Specific Survival		Relapse Free Survival	
	Multivariate Hazards ratio (95% CI)	p-value	Univariate Hazards ratio (95% CI)	p-value
Pathological tumor stage				
Stage 1 - 3b vs. 3c - 4b	5.66 (2.467-13.012)	<0.0001	5.192 (1.860-14.496)	0.0017
Tumor grade				
BL and G1 vs. G2 and G3	4.919 (2.080-11.633)	0.0003	7.989 (2.385-26.760)	0.0008
Age				
<50 vs. ≥50	0.951 (0.482-1.877)	0.8853		
Residual Disease				
RD<1cm vs. ≥1cm	2.974 (1.783-4.959)	<0.0001	2.779 (1.433-5.393)	0.0025
CA125 level at diagnosis				
CA125 <500 vs. >500 U/ml	1.148 (0.625-2.109)	0.6563	1.289 (0.659-2.520)	0.4587
Performance Status				
PS<1 vs. ≥1	0.286 (0.136-0.601)	0.0009		
CLDN3 expression				
Membranous Score 0 vs. >0	1.165 (0.325-4.183)	0.8145		
Membranous Score <1 vs. ≥1			0.953 (0.473-1.919)	0.8918
CA125 expression				
Membranous apical Score 0 vs. >0	0.917 (0.415-2.025)	0.8302	0.693 (0.271-1.768)	0.4427
Membranous apical Score <1 vs. ≥1	1.664 (0.976-2.837)	0.0612		
MUC1 expression				
Membranous apical Score 0 vs. >0				
Membranous apical Score <1 vs. ≥1	0.678 (0.255-1.804)	0.4361		
Membranous apical Score <2 vs. ≥2				

WE CLAIM:

1. A method of detecting an ovarian cancer-associated transcript in a biological sample, the method comprising contacting the biological sample with a polynucleotide
5 that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Table 1 or 2 or 3.
2. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being
10 tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a modified level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a
15 sequence selected from the group consisting of:
 - (i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
 - 20 (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
 - 25 (iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
 - (iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 47, 49, 51, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and
 - 30 (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

3. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a modified level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:
- 5
- (i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
 - (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
 - (iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 1, 5, 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
 - (iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 6, 8, 10, 12, 14, 16, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 47, 49, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and
 - (v) a sequence that is complementary to (i) or (ii) or (iii) or (iv).
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4. The method of claim 2 or 3 wherein the hybridization is enhanced in the sample from the subject being tested compared to the hybridization obtained for a sample from a control subject not having ovarian cancer.
5. The method of claim 2 or 3 wherein the hybridization is reduced in the sample from the subject being tested compared to the hybridization obtained for a sample from a control subject not having ovarian cancer.

6. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an enhanced level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- 10 (i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;
- 15 (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;
- (iii) a sequence that is at least about 80% identical to (i) or (ii);
- 20 (iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200; and
- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

25

7. The method of claim 6 wherein the nucleic acid probe comprises a sequence selected from the group consisting of:

- 30 (i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;

35

- (iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 7, 9, 11, 13, 15, 17, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 45, 46, 48, 52, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- 5 (iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 8, 10, 12, 14, 16, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 47, 49, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and
- (v) a sequence that is complementary to any one of the sequences set forth in (i) or
10 (ii) or (iii) or (iv).

8. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for
15 hybridization to occur and then detecting the hybridization wherein a reduced level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- 20 (i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1
25 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200;
- (iii) a sequence that is at least about 80% identical to (i) or (ii);
- (iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of
30 NM_022117, NM_005460, NM_002387, AI745249 and AI694200; and
- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

9. The method of claim 8 wherein the nucleic acid probe comprises a sequence
35 selected from the group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, and 5;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 1, 3, and 5;
- (iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 1, 3, and 5;
- (iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 2, 4, and 6; and
- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

10. The method according to any one of claims 1 to 9 wherein the ovarian cancer that is diagnosed is an epithelial ovarian cancer.

11. The method according to any one of claims 1 to 9 wherein the ovarian cancer that is diagnosed is selected from the group consisting of serous ovarian cancer, non-invasive ovarian cancer, mixed phenotype ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer, clear cell ovarian cancer, papillary serous ovarian cancer, Brenner cell and undifferentiated adenocarcinoma.

12. The method according to claim 11 wherein the ovarian cancer that is diagnosed is selected from the group consisting of serous ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer and clear cell ovarian cancer.

13. A method of diagnosing a serous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein a modified level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a serous ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession

Number selected from the group consisting of: U62801, D49441, X51630, And AB018305;

- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession Number selected from the group consisting of: U62801, D49441, X51630, And AB018305;
- (iii) a sequence that is at least about 80% identical to (i) or (ii);
- (iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession Number selected from the group consisting of: U62801, D49441, X51630, And AB018305; and
- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

14. A method of diagnosing a mucinous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a mucinous ovarian cancer, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063, AI073913, AI928445, NM_022454, W40460, AA132961 and AF111856;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063, AI073913, AI928445, NM_022454, W40460, AA132961 and AF111856;
- (iii) a sequence that is at least about 80% identical to (i) or (ii);
- (iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063, AI073913, AI928445, NM_022454, W40460, AA132961 and AF111856; and

- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

15. The method of claim 14 wherein the nucleic acid probe comprises a sequence
5 selected from the group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from SEQ ID NO: 57 or 59 or 61;
(ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from SEQ ID NO: 57 or 59 or 61;
10 (iii) a sequence that is at least about 80% identical to SEQ ID NO: 57 or 59 or 61;
(iv) a sequence that encodes the amino acid sequence set forth in SEQ ID NO: 58 or 60 or 62; and
(v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

15

16. The method according to any one of claims 1 to 15 comprising performing a PCR reaction.

17. The method according to any one of claims 1 to 16 comprising performing a
20 nucleic acid hybridization.

18. A method of detecting an ovarian cancer-associated polypeptide in a biological sample the method comprising contacting the biological sample with an antibody that binds specifically to an ovarian cancer-associated polypeptide in the biological sample,
25 the polypeptide being encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3.

19. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being
30 tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a modified level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a
35 polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence

selected from the group consisting of SEQ ID NOs: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 47, 49, 51, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

- 5 20. The method of claim 19 wherein the antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 2, 6, 8, 10, 12, 14, 16, 18, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 47, 49, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

10

21. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the
15 antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a polypeptide encoded by a nucleic acid set forth in
20 Table 1 or 2 other than a nucleic acid having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200.

22. The method of claim 21 wherein the antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of
25 a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 47, 49, 51, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

23. A method of diagnosing an ovarian cancer in a human or animal subject being
30 tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a reduced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that
35 the subject being tested has an ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous

amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of NM_022117, NM_005460, NM_002387, AI745249 and AI694200.

- 5 24. The method of claim 23 wherein the antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 2, 4, and 6.
- 10 25. The method according to any one of claims 19 to 24 wherein the ovarian cancer that is diagnosed is an epithelial ovarian cancer.
- 15 26. The method according to any one of claims 19 to 24 wherein the ovarian cancer that is diagnosed is selected from the group consisting of serous ovarian cancer, non-invasive ovarian cancer, mixed phenotype ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer, clear cell ovarian cancer, papillary serous ovarian cancer, Brenner cell and undifferentiated adenocarcinoma.
- 20 27. The method according to claim 26 wherein the ovarian cancer that is diagnosed is selected from the group consisting of serous ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer and clear cell ovarian cancer.
- 25 28. A method of diagnosing a serous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a modified level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a serous ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 2 or as set forth in Table 1 and having an Accession Number selected from the group consisting of: U62801, D49441, X51630, And AB018305.
- 30 29. A method of diagnosing a mucinous ovarian cancer in a human or animal subject being tested said method comprising contacting a biological sample from said subject

being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein a reduced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer

5 indicates that the subject being tested has a mucinous ovarian cancer, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a polypeptide encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_006149, AA315933, U47732, NM_005588, AW503395, NM_004063, AI073913,

10 AI928445, NM_022454, W40460, AA132961 and AF111856.

30. The method according to claim 29 wherein the antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence having at least about 80% identity to SEQ ID NO: 58 or 60 or 62.

15

31. A method of detecting an ovarian cancer-associated antibody in a biological sample the method comprising contacting the biological sample with a polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3, wherein the polypeptide specifically

20 binds to the ovarian cancer-associated antibody.

32. The method according to any one of claims 1 to 31 wherein the biological sample is contacted with a plurality of nucleic acid probes and/or antibodies and/or polypeptides.

25 33. The method according to any one of claims 1 to 32 wherein the subject being tested is a patient undergoing a therapeutic regimen to treat ovarian cancer.

34. The method according to any one of claims 1 to 32 wherein the subject being tested is a subject suspected of having ovarian cancer.

30

35. A method of monitoring the efficacy of a therapeutic treatment of ovarian cancer, the method comprising:

- (i) providing a biological sample from a patient undergoing the therapeutic treatment; and
- 35 (ii) determining the level of a ovarian cancer-associated transcript in the biological sample by contacting the biological sample with a polynucleotide

that selectively hybridizes to a sequence having at least about 80% identity to a sequence as shown in any one of Tables 1-3, thereby monitoring the efficacy of the therapy.

5 36. The method according to claim 35 further comprising comparing the level of the ovarian cancer-associated transcript to a level of the ovarian cancer-associated transcript in a biological sample from the patient prior to, or earlier in, the therapeutic treatment.

10 37. A method of monitoring the efficacy of a therapeutic treatment of ovarian cancer, the method comprising :

(i) providing a biological sample from a patient undergoing the therapeutic treatment; and

15 (ii) determining the level of a ovarian cancer-associated antibody in the biological sample by contacting the biological sample with a polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3, wherein the polypeptide specifically binds to the ovarian cancer-associated antibody, thereby monitoring the efficacy of the therapy.

20 38. The method of claim 37 further comprising comparing the level of the ovarian cancer-associated antibody to a level of the ovarian cancer-associated antibody in a biological sample from the patient prior to, or earlier in, the therapeutic treatment.

25 39. A method of monitoring the efficacy of a therapeutic treatment of ovarian cancer, the method comprising :

(i) providing a biological sample from a patient undergoing the therapeutic treatment; and

30 (ii) determining the level of a ovarian cancer-associated polypeptide in the biological sample by contacting the biological sample with an antibody, wherein the antibody specifically binds to a polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3, thereby monitoring the efficacy of the therapy.

40. The method of claim 39 further comprising comparing the level of the ovarian cancer-associated polypeptide to a level of the ovarian cancer-associated polypeptide in a biological sample from the patient prior to, or earlier in, the therapeutic treatment.
- 5 41. The method according to any one of claims 35 to 40 wherein the ovarian cancer that is diagnosed is an epithelial ovarian cancer.
42. The method according to any one of claims 35 to 41 wherein the ovarian cancer that is diagnosed is selected from the group consisting of serous ovarian cancer, non-
10 invasive ovarian cancer, mixed phenotype ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer, clear cell ovarian cancer, papillary serous ovarian cancer, Brenner cell and undifferentiated adenocarcinoma.
43. The method according to claim 42 wherein the ovarian cancer that is diagnosed is
15 selected from the group consisting of serous ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer and clear cell ovarian cancer.
44. A method of determining the likelihood of survival of a subject suffering from an ovarian cancer, said method comprising contacting a biological sample from said subject
20 being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said nucleic acid probe comprises a
25 sequence selected from the group consisting of:
- (i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713,
30 X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761, AW968613, AW972565, AF045229, AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602, AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417,
35 L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135, BE466173, AI354722, M90464, AA829286, AI333771, BE465867, NM_014992,

- BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122, AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955;
- 5 (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of:
- 10 NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761, AW968613, AW972565, AF045229, AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602, AJ245210, X65965,
- 15 AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135, BE466173, AI354722, M90464, AA829286, AI333771, BE465867, NM_014992, BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122,
- 20 AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955;
- (iii) a sequence that is at least about 80% identical to (i) or (ii);
- (iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in
- 25 Table 1 and having an Accession Number selected from the group consisting of:
- NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761,
- 30 AW968613, AW972565, AF045229, AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602, AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135, BE466173, AI354722, M90464, AA829286, AI333771, BE465867, NM_014992, BE616902, AA430373,
- 35 R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122,

AB001914, AA311919, AI381750, AA292998, BE439580, AI677897, N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955; and

- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

45. The method of claim 44 wherein the nucleic acid probe comprises a sequence selected from the group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 63, 65, 67, 69, 71, and 73;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a sequence selected from the group consisting of SEQ ID NOs: 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- (iii) a sequence that is at least about 80% identical to a sequence selected from the group consisting of SEQ ID NOs: 63, 65, 67, 69, 71, 73, 75, 77, 79, 81 and 83;
- (iv) a sequence that encodes an amino acid sequence selected from the group consisting of SEQ ID NOs: 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84; and
- (v) a sequence that is complementary to (i) or (ii) or (iii) or (iv).

46. A method of determining the likelihood of survival of a subject suffering from an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: NM_003014, AA046217, NM_015902, T83882, AB040888, AA628980, AI623351, AW614420, AA243499, AF251237, AI970797, AF145713, X78565, T97307, BE243845, AW068302, AL133561, BE313555, X07820, AI973016, AF084545, U41518, Z11894, AW138190, BE086548, W47196, AI796870, X02761, AW968613, AW972565, AF045229, AW953853, U52426, F06700, AI798863, H52761, BE546947, AU076643, U20536, AA581602, AJ245210, X65965, AI806770, BE386490, AW581992, U77534, AL034417, L10343, AW518944, W28729, AI640160, U11862, AW295980, X59135,

BE466173, AI354722, M90464, AA829286, AI333771, BE465867, NM_014992, BE616902, AA430373, R27430, BE387335, AW264102, AW952323, AA088177, BE614567, AL079658, NM_002776, BE261944, NM_006379, AI002238, X81789, NM_002122, AB001914, AA311919, AI381750, AA292998, BE439580, AI677897,
 5 N72403, BE003054, AL035588, AI080491, AW770994, H24177, AF146761, NM_001955, AI680737, AI752666, AA505445, BE246649, and NM_003955.

47. The method of claim 46 wherein the antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of
 10 a sequence having at least about 80% identity to a sequence selected from the group consisting of SEQ ID NOs: 64, 66, 68, 70, 72, 74, 76, 78, 80, 82 and 84.

48. A method of determining the likelihood of survival of a subject suffering from a serous ovarian cancer, said method comprising contacting a biological sample from said
 15 subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization obtained for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said nucleic acid probe comprises a
 20 sequence selected from the group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid comprising the nucleotide sequence set forth in SEQ ID NO: 71 or 73;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid comprising the
 25 nucleotide sequence set forth in SEQ ID NO: 71 or 73;
- (iii) a sequence that is at least about 80% identical to (i) or (ii) and encoding an sFRP protein or a SOCS3 protein;
- (iv) a sequence that encodes a polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 72 or 74; and
- 30 (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

49. A method of determining the likelihood of survival of a subject suffering from a serous ovarian cancer, said method comprising contacting a biological sample from said
 35 subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced

level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein said antibody binds to an sFRP polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 72 or a SOCS3 polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 74.

50. A method of determining the likelihood of survival of a subject suffering from a serous ovarian cancer, said method comprising contacting a biological sample from said subject being tested with at least two antibodies for a time and under conditions sufficient for antigen-antibody complexes to form and then detecting the complexes wherein an enhanced level of the antigen-antibody complexes for the subject being tested compared to the amount of the antigen-antibody complexes formed for a control subject not having ovarian cancer indicates that the subject being tested has a poor probability of survival, and wherein one antibody binds to an sFRP polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 72 and wherein one antibody binds to a SOCS3 polypeptide comprising the amino acid sequence set forth in SEQ ID NO: 74.

51. The method according to any one of claims 44 to 47 wherein the ovarian cancer is an epithelial ovarian cancer.

52. The method according to any one of claims 44 to 47 wherein the ovarian cancer is selected from the group consisting of serous ovarian cancer, non-invasive ovarian cancer, mixed phenotype ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer, clear cell ovarian cancer, papillary serous ovarian cancer, Brenner cell and undifferentiated adenocarcinoma.

53. The method according to claim 52 wherein the ovarian cancer is selected from the group consisting of serous ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer and clear cell ovarian cancer.

54. A method of determining the likelihood that a subject will suffer from a recurrence of an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with a nucleic acid probe for a time and under conditions sufficient for hybridization to occur and then detecting the hybridization wherein an elevated level of hybridization of the probe for the subject being tested compared to the hybridization

obtained for a control subject not having ovarian cancer indicates that the subject being tested has a high probability of recurrence, and wherein said nucleic acid probe comprises a sequence selected from the group consisting of:

- (i) a sequence comprising at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: M86849, AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343, NM_002514, AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393, H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512, AW953853, AU076611, AW968613, AL353944, BE614149, AA292998, H12912, AA188763, AK000596, AI970797, AW519204, Z42387, AF145713, AA972412, AK001564, AW959861, BE313555, W25005, AI193356, AF111106, AI130740, AA985190, BE221880, AF084545, R26584, AW247380, AA364261, U25849, AF262992, AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237, NM_000636, AA130986, AA216363, AA628980, AA811657, AA897108, AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248, AK002039, AL109791, AW090198, AW296454, AW445034, AW452948, AW470411, AW885727, AW970859, AW979189, BE165866, BE175582, BE242587, BE271927, BE439580, BE464016, D63216, F34856, M83822, N33937, N49068, N51357, N80486, NM_000954, NM_005756, NM_016652, R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and Z45051,
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to at least about 20 contiguous nucleotides from a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: M86849, AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343, NM_002514, AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393,

H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446,
 AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, BE464341,
 AL080235, AI557212, X75208, AA628980, BE242587, NM_005512, AW953853,
 AU076611, AW968613, AL353944, BE614149, AA292998, H12912, AA188763,
 5 AK000596, AI970797, AW519204, Z42387, AF145713, AA972412, AK001564,
 AW959861, BE313555, W25005, AI193356, AF111106, AI130740, AA985190,
 BE221880, AF084545, R26584, AW247380, AA364261, U25849, AF262992,
 AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237,
 NM_000636, AA130986, AA216363, AA628980, AA811657, AA897108,
 10 AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248,
 AK002039, AL109791, AW090198, AW296454, AW445034, AW452948,
 AW470411, AW885727, AW970859, AW979189, BE165866, BE175582,
 BE242587, BE271927, BE439580, BE464016, D63216, F34856, M83822,
 N33937, N49068, N51357, N80486, NM_000954, NM_005756, NM_016652,
 15 R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and
 Z45051;

- (iii) a sequence that is at least about 80% identical to (i) or (ii);
- (iv) a sequence that encodes a polypeptide encoded by a nucleic acid set forth in
 Table 1 and having an Accession Number selected from the group consisting
 20 of: M86849, AW963419, BE298665, AK000637, BE077546, T97307, R24601,
 BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239,
 BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573,
 BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343,
 NM_002514, AI863735, NM_005397, W26391, H15474, U51166, AA243499,
 25 AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730,
 AF007393, H65423, N46243, AA095971, U20350, NM_005756, D19589,
 AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863,
 BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512,
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- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

55. The method of claim 54 determining the likelihood that a subject will suffer from a recurrence of an ovarian cancer, said method comprising contacting a biological sample from said subject being tested with an antibody for a time and under conditions sufficient for an antigen-antibody complex to form and then detecting the complex wherein an enhanced level of the antigen-antibody complex for the subject being tested compared to the amount of the antigen-antibody complex formed for a control subject not having ovarian cancer indicates that the subject being tested has a high probability of recurrence, and wherein said antibody binds to a polypeptide comprising an amino acid sequence comprising at least about 10 contiguous amino acid residues of a sequence encoded by a nucleic acid set forth in Table 1 and having an Accession Number selected from the group consisting of: M86849, AW963419, BE298665, AK000637, BE077546, T97307, R24601, BE090176, AA393907, W28729, BE313754, AW673081, AA356694, L08239, BE397649, NM_012317, NM_000947, AJ250562, AL040183, BE207573, BE564162, BE439580, AW067800, AA569756, AW138190, AF126245, L10343, NM_002514, AI863735, NM_005397, W26391, H15474, U51166, AA243499, AW408807, AI738719, AB040888, BE313077, AI677897, C14898, AI821730, AF007393, H65423, N46243, AA095971, U20350, NM_005756, D19589, AW957446, AW294647, BE159718, AI888490, AA022569, BE147740, AI798863, BE464341, AL080235, AI557212, X75208, AA628980, BE242587, NM_005512, AW953853, AU076611, AW968613, AL353944, BE614149, AA292998, H12912, AA188763, AK000596, AI970797, AW519204, Z42387, AF145713, AA972412, AK001564, AW959861, BE313555, W25005, AI193356, AF111106, AI130740, AA985190, BE221880, AF084545, R26584, AW247380, AA364261, U25849, AF262992, AW342140, AL133572, AI497778, AI745379, U51712, AW375974, AF251237, NM_000636, AA130986, AA216363, AA628980, AA811657, AA897108, AB040888, AF212225, AI089575, AI282028, AI368826, AI718702, AI827248, AK002039, AL109791, AW090198, AW296454, AW445034, AW452948, AW470411, AW885727, AW970859, AW979189, BE165866, BE175582, BE242587, BE271927, BE439580,

BE464016, D63216, F34856, M83822, N33937, N49068, N51357, N80486, NM_000954, NM_005756, NM_016652, R26584, R31178, W05391, W25005, W45393, W68815, X65965, X76732 and Z45051.

- 5 56. The method according to claim 54 or 55 wherein the ovarian cancer is an epithelial ovarian cancer.

57. The method according to any one of claims 54 to 56 wherein the ovarian cancer is selected from the group consisting of serous ovarian cancer, non-invasive ovarian
10 cancer, mixed phenotype ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer, clear cell ovarian cancer, papillary serous ovarian cancer, Brenner cell and undifferentiated adenocarcinoma.

58. The method according to claim 57 wherein the ovarian cancer is selected from the
15 group consisting of serous ovarian cancer, mucinous ovarian cancer, endometrioid ovarian cancer and clear cell ovarian cancer.

59. The method according to any one of claims 35 to 58 wherein the biological sample is contacted with a plurality of nucleic acid probes and/or antibodies and/or polypeptides.

20

60. A method for identifying a compound that modulates an ovarian cancer-associated polypeptide, the method comprising :

- (i) contacting the compound with a ovarian cancer-associated polypeptide, the polypeptide encoded by a polynucleotide that selectively hybridizes to a sequence
25 at least 80% identical to a sequence as shown in Tables 1-3; and
(ii) determining the functional effect of the compound upon the polypeptide.

61. A method for determining a candidate compound for the treatment of ovarian cancer comprising :

- 30 (i) administering a test compound to a mammal having ovarian cancer or a cell isolated therefrom;
(ii) comparing the level of gene expression of a polynucleotide that selectively hybridizes to a sequence at least 80% identical to a sequence as shown in Tables 1-3 in a treated cell or mammal with the level of gene expression of the
35 polynucleotide in a control cell or mammal, wherein a test compound that

modulates the level of expression of the polynucleotide is a candidate for the treatment of ovarian cancer.

5 62. An assay device for use in the diagnosis or prognosis of ovarian cancer, said device comprising a plurality of polynucleotides immobilized to a solid phase, wherein each of said polynucleotides consists of a gene as listed in any one of Tables 1-3.

63. The device of claim 62 consisting of a substantially planar chip.

10 64. An assay device for use in the diagnosis or prognosis of ovarian cancer, said device comprising a plurality of different antibodies immobilized to a solid phase, wherein each of said antibodies binds to a polypeptide listed in Tables 1-3.

65. The device of claim 64 consisting of a substantially planar chip.

15

66. Use of a polynucleotide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

20 67. Use of a vector comprising a polynucleotide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

25 68. Use of an isolated polypeptide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

30 69. Use of an antibody that binds to an isolated polypeptide as set forth in any one of Tables 1-3 in the diagnosis or prognosis of ovarian cancer or for the preparation of a medicament for the treatment of ovarian cancer.

70. A method of diagnosing an ovarian cancer in a human or animal subject being tested said method comprising determining aberrant methylation in a promoter sequence that regulates expression of a tumor suppressor gene in a biological sample from said
35 subject compared to the methylation of the promoter in nucleic acid obtained for a control

subject not having ovarian cancer wherein said aberrant methylation indicates that the subject being tested has an ovarian ovarian cancer.

5 71. The method of claim 70 wherein hypermethylation of the promoter sequence is determined.

72. The method of claim 70 or 71 wherein the methylation is determined in the promoter region that regulates expression of an MCC gene comprising a sequence selected from the group consisting of:

- 10 (i) the nucleotide sequence set forth as SEQ ID NO: 3;
- (ii) a sequence that hybridizes under at least low stringency hybridization conditions to the nucleotide sequence set forth as SEQ ID NO: 3;
- (iii) a sequence that is at least about 80% identical to (i) or (ii);
- 15 (iv) a sequence that encodes a polypeptide encoded by a nucleotide sequence set forth as SEQ ID NO: 3; and
- (v) a sequence that is complementary to any one of the sequences set forth in (i) or (ii) or (iii) or (iv).

20 73. The method according to any one of claims 70 to 72 wherein the ovarian cancer that is diagnosed is an epithelial ovarian cancer.

1/5

Claudin 3

EP-CAM

SOX17

CA125

MUC-1

E-cadherin

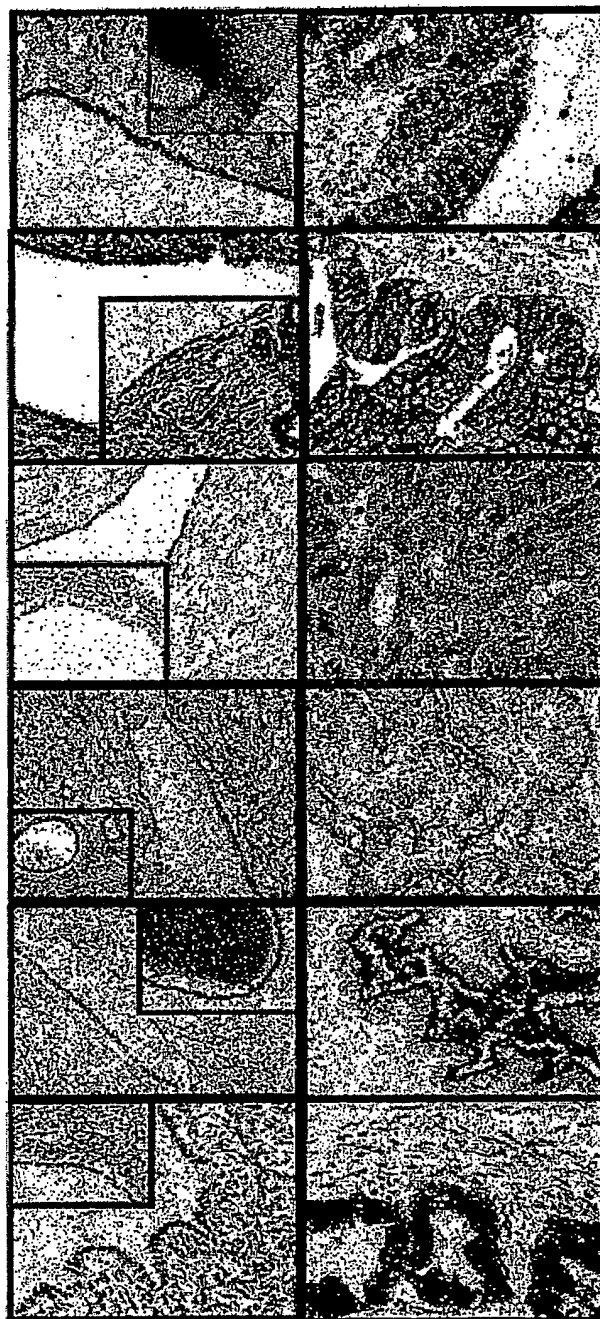


FIGURE 1

2/5

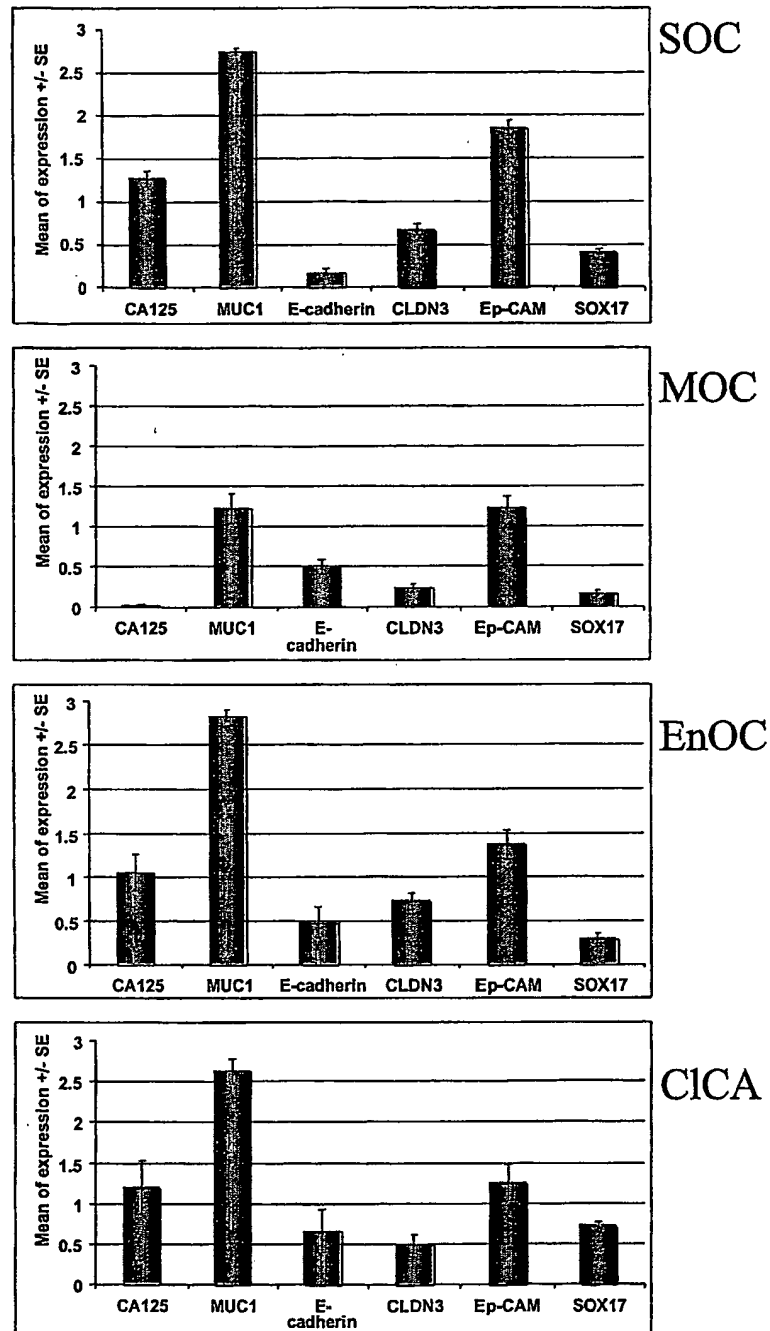


FIGURE 2

3/5

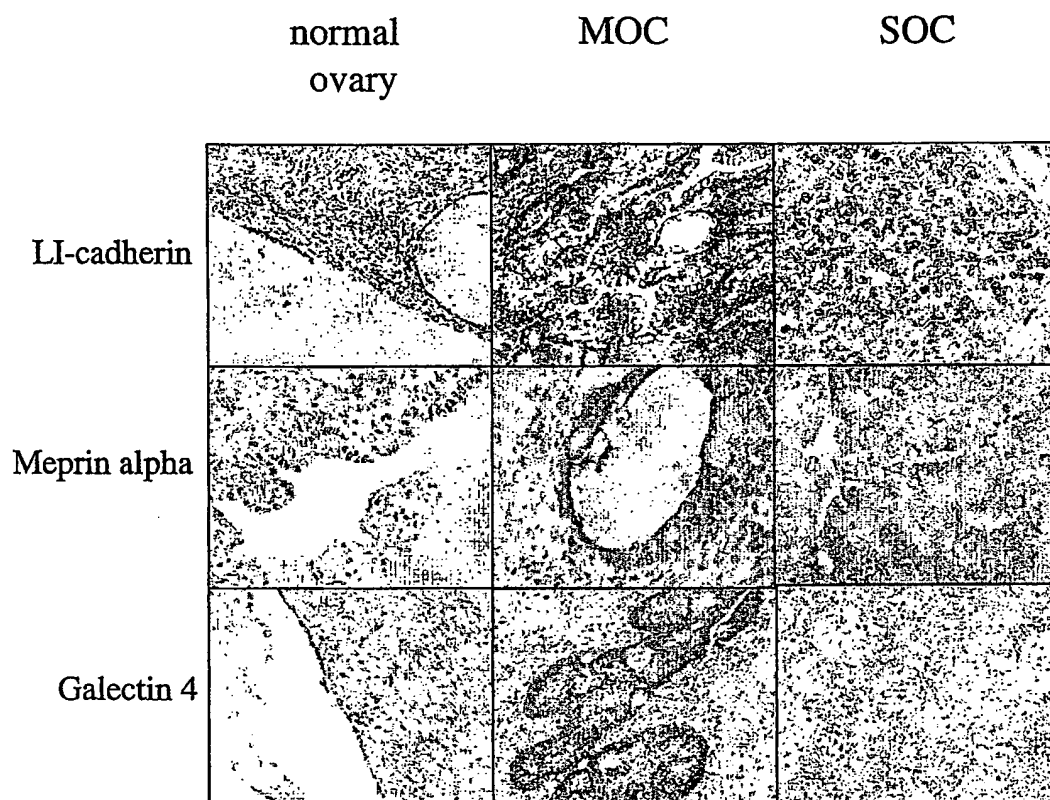


FIGURE 3

4/5

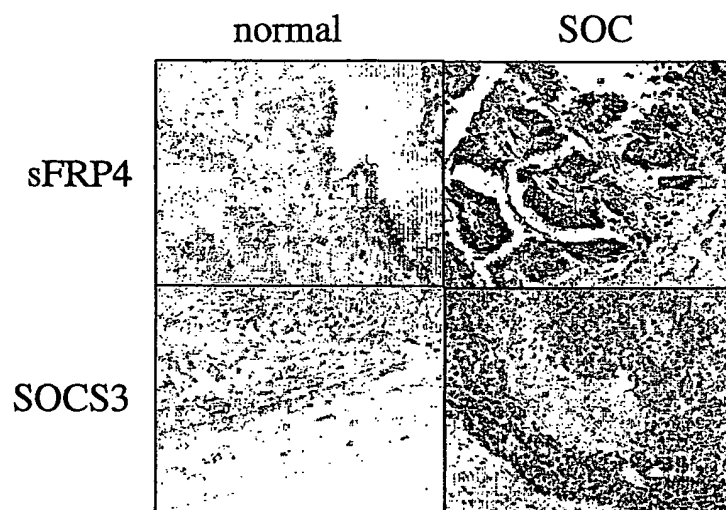


FIGURE 4a

5/5

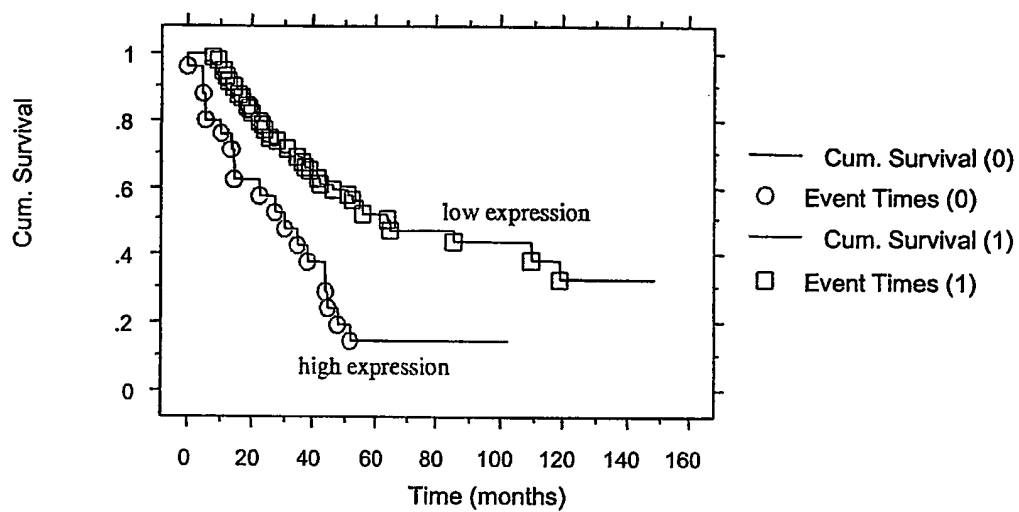


FIGURE 4b

SEQUENCE LISTING

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<151> 2002-09-05

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 1 5

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 Asp Leu Asp Glu Ile Asp Phe Ser Asp Asp Ile Ser Tyr Ser Val Thr
 10 15 20

tca ctc aag acg atc cca gaa ctg tgc cga aga tgt gat acg caa aac 210
 Ser Leu Lys Thr Ile Pro Glu Leu Cys Arg Arg Cys Asp Thr Gln Asn
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gaa gac aga tca gct tct agc tct agc tgg aat tgt ggc atc tca act 258
 Glu Asp Arg Ser Ala Ser Ser Ser Ser Trp Asn Cys Gly Ile Ser Thr
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ctt att aca aac acg caa aag ccc aca gga atc gct gat gtg tac agt 306
 Leu Ile Thr Asn Thr Gln Lys Pro Thr Gly Ile Ala Asp Val Tyr Ser
 60 65 70

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 Lys Phe Arg Pro Val Lys Arg Val Ser Pro Leu Lys His Gln Pro Glu
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act ctg gag aac aat gaa agt gat gac caa aag aac cag aaa gtg gtt 402
 Thr Leu Glu Asn Asn Glu Ser Asp Asp Gln Lys Asn Gln Lys Val Val
 90 95 100

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 Glu Tyr Gln Lys Gly Gly Glu Ser Asp Leu Gly Pro Gln Pro Gln Glu
 105 110 115

ctt ggc cct gga gat gga gtg ggc ggc cca cca ggt aag agc tct gag 498
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 Gly Ile Ala Asp Val Tyr Ser Lys Phe Arg Pro Val Lys Arg Val Ser
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Leu Glu Lys Arg Glu Leu Lys Leu Ala Arg Leu Arg Gln Leu Met Gln
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Lys Thr Thr Pro Val Arg Lys Ala Asp Arg Pro Arg Pro Gln Pro Ile
 690 695 700

Val Glu Ser Val Glu Ser Met Asp Ser Ala Glu Ser Leu His Leu Met
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Ile Lys Lys His Thr Leu Ala Ser Gly Gly Arg Arg Phe Pro Phe Ser
 725 730 735

Ile Lys Ala Ser Lys Ser Leu Asp Gly His Ser Pro Ser Pro Thr Ser
740 745 750

Glu Ser Ser Glu Pro Asp Leu Glu Ser Gln Tyr Pro Gly Ser Gly Ser
755 760 765

Ile Pro Pro Asn Gln Pro Ser Gly Asp Pro Gln Gln Pro Ser Pro Asp
770 775 780

Ser Thr Ala Ala Gln Lys Val Ala Thr Ser Pro Lys Ser Ala Leu Lys
785 790 795 800

Ser Pro Ser Ser Lys Arg Arg Thr Ser Gln Asn Leu Lys Leu Arg Val
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Thr Phe Glu Glu Pro Val Val Gln Met Glu Gln Pro Ser Leu Glu Leu
820 825 830

Asn Gly Glu Lys Asp Lys Asp Lys Gly Arg Thr Leu Gln Arg Thr Ser
835 840 845

Thr Ser Asn Glu Ser Gly Asp Gln Leu Lys Arg Pro Phe Gly Ala Phe
850 855 860

Arg Ser Ile Met Glu Thr Leu Ser Gly Asn Gln Asn Asn Asn Asn Asn
865 870 875 880

Tyr Gln Ala Ala Asn Gln Leu Lys Thr Ser Thr Leu Pro Leu Thr Ser
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Lys Gly Lys Asn Lys Ala Ala
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Met Asn Ser Gly Val	
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Ala Met Lys Tyr Gly Asn Asp Ser Ser Ala Glu Leu Ser Glu Leu His	
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Ser Ala Ala Leu Ala Ser Leu Lys Gly Asp Ile Val Glu Leu Asn Lys	
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Arg Leu Gln Gln Thr Glu Arg Glu Arg Asp Leu Leu Glu Lys Lys Leu	
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Ala Lys Ala Gln Cys Glu Gln Ser His Leu Met Arg Glu His Glu Asp	
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gtc cag gag cga acg acg ctt cgc tat gag gaa cgc atc aca gag ctc	475
Val Gln Glu Arg Thr Thr Leu Arg Tyr Glu Glu Arg Ile Thr Glu Leu	
70 75 80 85	
cac agc gtc att gcg gag ctc aac aag aag ata gac cgt ctg caa gcc	523
His Ser Val Ile Ala Glu Leu Asn Lys Lys Ile Asp Arg Leu Gln Gly	
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Thr Thr Ile Arg Glu Glu Asp Glu Tyr Ser Glu Leu Arg Ser Glu Leu	
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Ser Gln Ser Gln His Glu Val Asn Glu Asp Ser Arg Ser Met Asp Gln	
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Asp Gln Thr Ser Val Ser Ile Pro Glu Asn Gln Ser Thr Met Val Thr	
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Ala Asp Met Asp Asn Cys Ser Asp Leu Asn Ser Glu Leu Gln Arg Val	
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Leu Thr Gly Leu Glu Asn Val Val Cys Gly Arg Lys Lys Ser Ser Cys	
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Ser Leu Ser Val Ala Glu Val Asp Arg His Ile Glu Gln Leu Thr Thr	
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Ala Ser Glu His Cys Asp Leu Ala Ile Lys Thr Val Glu Glu Ile Glu	
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act gcc atg ctg tgc agc aaa gag gaa gaa ctg aac cgg act aag gcc Thr Ala Met Leu Cys Ser Lys Glu Glu Glu Leu Asn Arg Thr Lys Ala 250 255 260	1003
acc atg aat gcc atc cgg gaa gag cgg gac cgg ctc cgg agg cgg gtc Thr Met Asn Ala Ile Arg Glu Glu Arg Asp Arg Leu Arg Arg Arg Val 265 270 275	1051
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Arg Glu His Glu Asp Val Gln Glu Arg Thr Thr Leu Arg Tyr Glu Glu
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Arg Ile Thr Glu Leu His Ser Val Ile Ala Glu Leu Asn Lys Lys Ile
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Asp Arg Leu Gln Gly Thr Thr Ile Arg Glu Glu Asp Glu Tyr Ser Glu
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Leu Arg Ser Glu Leu Ser Gln Ser Gln His Glu Val Asn Glu Asp Ser
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Arg Ser Met Asp Gln Asp Gln Thr Ser Val Ser Ile Pro Glu Asn Gln
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Ser Thr Met Val Thr Ala Asp Met Asp Asn Cys Ser Asp Leu Asn Ser
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Glu Leu Gln Arg Val Leu Thr Gly Leu Glu Asn Val Val Cys Gly Arg
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Lys Lys Ser Ser Cys Ser Leu Ser Val Ala Glu Val Asp Arg His Ile
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Glu Gln Leu Thr Thr Ala Ser Glu His Cys Asp Leu Ala Ile Lys Thr
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Val Glu Glu Ile Glu Gly Val Leu Gly Arg Asp Leu Tyr Pro Asn Leu
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Ala Glu Glu Arg Ser Arg Trp Glu Lys Glu Leu Ala Gly Leu Arg Glu
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Glu Asn Glu Ser Leu Thr Ala Met Leu Cys Ser Lys Glu Glu Glu Leu
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Asn Arg Thr Lys Ala Thr Met Asn Ala Ile Arg Glu Glu Arg Asp Arg
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Leu Arg Arg Arg Val Arg Glu Leu Gln Thr Arg Leu Gln Ser Val Gln
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Ala Thr Gly Pro Ser Ser Pro Gly Arg Leu Thr Ser Thr Asn Arg Pro
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Ile Asn Pro Ser Thr Gly Glu Leu Ser Thr Ser Ser Ser Ser Asn Asp
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Ile Pro Ile Ala Lys Ile Ala Glu Arg Val Lys Leu Ser Lys Thr Arg
325 330 335

Ser Glu Ser Ser Ser Ser Asp Arg Pro Val Leu Gly Ser Glu Ile Ser
340 345 350

Ser Ile Gly Val Ser Ser Ser Val Ala Glu His Leu Ala His Ser Leu
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Gln Asp Cys Ser Asn Ile Gln Glu Ile Phe Gln Thr Leu Tyr Ser His
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Gly Ser Ala Ile Ser Glu Ser Lys Ile Arg Glu Phe Glu Val Glu Thr
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Glu Arg Leu Asn Ser Arg Ile Glu His Leu Lys Ser Gln Asn Asp Leu
405 410 415

Leu Thr Ile Thr Leu Glu Glu Cys Lys Ser Asn Ala Glu Arg Met Ser
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Met Leu Val Gly Lys Tyr Glu Ser Asn Ala Thr Ala Leu Arg Leu Ala
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Leu Gln Tyr Ser Glu Gln Cys Ile Glu Ala Tyr Glu Leu Leu Leu Ala
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Gly Val Gly Ser Ser Pro Gly Asp Gln Ser Gly Asp Glu Asn Ile Thr
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Gln Met Leu Lys Arg Ala His Asp Cys Arg Lys Thr Ala Glu Asn Ala
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Lys Asn Asp Arg Ala Ala Val Lys Leu Thr Met Leu Glu Leu Glu Ser
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Ile His Ile Asp Pro Leu Ser Tyr Asp Val Lys Pro Arg Gly Asp Ser
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Gln Arg Leu Asp Leu Glu Asn Ala Val Leu Met Gln Glu Leu Met Ala
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Met Lys Glu Glu Met Ala Glu Leu Lys Ala Gln Leu Tyr Leu Leu Glu
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675 680 685

Ser Lys Asp Lys Pro Gly Lys Glu Cys Ala Asp Ala Ala Ser Pro Ala
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Ala Glu Phe Thr Asn Ala Ile Arg Arg Glu Lys Lys Leu Lys Ala Arg
725 730 735

Val Gln Glu Leu Val Ser Ala Leu Glu Arg Leu Thr Lys Ser Ser Glu
740 745 750

Ile Arg His Gln Gln Ser Ala Glu Phe Val Asn Asp Leu Lys Arg Ala
755 760 765

Asn Ser Asn Leu Val Ala Ala Tyr Glu Lys Ala Lys Lys Lys His Gln
 770 775 780

Asn Lys Leu Lys Lys Leu Glu Ser Gln Met Met Ala Met Val Glu Arg
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 Met Asp Arg Pro Asp Glu Gly Pro Pro Ala Lys Thr Arg Arg
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ccg ccg ccg ctc ctc cga ctg ccg ctg cct cca ccc cag cag cgc ccg 267
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 Arg Leu Gln Glu Glu Thr Glu Ala Ala Gln Val Leu Ala Asp Met Arg
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 Pro Gly Trp Asp Ser Thr Ile Glu Ser Gly Tyr Gly Glu Ala Pro Pro

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Gln Leu Asp Leu Glu Ala Val Asn Ile Lys Ala Gly Lys Ala Phe Leu				
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gtg ata gag atc atc tca gac gaa tca gtg gaa gaa gag ggc att gag Val Ile Glu Ile Ile Ser Asp Glu Ser Val Glu Glu Glu Gly Ile Glu 625 630 635			2043
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635

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			M e t	M e t	G l y	G l y	G l u	S e r	A l a	A s p							
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L y s	A l a	T h r	A l a	A l a	A l a	A l a	A l a	A l a	S e r	L e u	L e u	A l a	A s n	G l y	H i s		
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c a c	a a a	a g t	g g t	g c t	g t g	g c c	a g c	c t g	c t g	a g c	a a g	g c a	g a g	c g g	g c c		1098
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a c g	g a g	c t g	g c a	g c c	g a g	g g a	c a g	c t g	a c g	c t g	c a g	c a g	t t t	g c g	c a g		1146
T h r	G l u	L e u	A l a	A l a	G l u	G l y	G l n	L e u	T h r	L e u	G l n	G l n	P h e	A l a	G l n		
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S e r	T h r	G l u	M e t	L e u	L y s	A r g	V a l	V a l	G l n	G l u	H i s	L e u	P r o	L e u	M e t		
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G l u	L e u	A l a	S e r	A l a	I l e	S e r	S e r	G l y	L y s	L y s	L y s	A r g	L y s	A r g	C y s		
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Ser Glu Pro Tyr Asn His Arg Phe Ser Asp Pro Glu Arg Val Asn Tyr
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Lys Phe Glu Ser Gly Thr Cys Ser Lys Met Glu Leu Ile Asp Asp Asn
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Leu Cys Leu Asn Ala Gln Gly Arg Arg Asn Gly Glu Ala Leu Val Arg
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Pro Thr Gly Asp Ala Phe Val Leu Phe Ala Cys Glu Glu Tyr Ala Gln
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Leu Gly Glu Phe Ala Thr Asp Ile Arg Thr His Gly Val His Met Val
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Phe Phe Phe Ser Leu Leu Phe Leu Gly Met Phe Leu Ser Gly Met Val
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Phe Ala Asp Cys Ile Ser Asp Glu Leu Pro Leu Gly Trp Glu Glu Ala
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 35 40 45

Asp Cys Ile Ser Asp Glu Leu Pro Leu Gly Trp Glu Glu Ala Tyr Asp
 50 55 60

Pro Gln Val Gly Asp Tyr Phe Ile Asp His Asn Thr Lys Thr Thr Gln
 65 70 75 80

Ile Glu Asp Pro Arg Val Gln Trp Arg Arg Glu Gln Glu His Met Leu
 85 90 95

Lys Asp Tyr Leu Val Val Ala Gln Glu Ala Leu Ser Ala Gln Lys Glu
 100 105 110

Ile Tyr Gln Val Lys Gln Gln Arg Leu Glu Leu Ala Gln Gln Glu Tyr
 115 120 125

Gln Gln Leu His Ala Val Trp Glu His Lys Leu Gly Ser Gln Val Ser
 130 135 140

Leu Val Ser Gly Ser Ser Ser Ser Ser Lys Tyr Asp Pro Glu Ile Leu
 145 150 155 160

Lys Ala Glu Ile Ala Thr Ala Lys Ser Arg Val Asn Lys Leu Lys Arg
 165 170 175

Glu Met Val His Leu Gln His Glu Leu Gln Phe Lys Glu Arg Gly Phe
 180 185 190

Gln Thr Leu Lys Lys Ile Asp Lys Lys Met Ser Asp Ala Gln Gly Ser
 195 200 205

Tyr Lys Leu Asp Glu Ala Gln Ala Val Leu Arg Glu Thr Lys Ala Ile
 210 215 220

Lys Lys Ala Ile Thr Cys Gly Glu Lys Glu Lys Gln Asp Leu Ile Lys
 225 230 235 240

Ser Leu Ala Met Leu Lys Asp Gly Phe Arg Thr Asp Arg Gly Ser His
 245 250 255

Ser Asp Leu Trp Ser Ser Ser Ser Ser Leu Glu Ser Ser Ser Phe Pro
 260 265 270

Leu Pro Lys Gln Tyr Leu Asp Val Ser Ser Gln Thr Asp Ile Ser Gly
 275 280 285

Ser Phe Gly Ile Asn Ser Asn Asn Gln Leu Ala Glu Lys Val Arg Leu
 290 295 300

Arg Leu Arg Tyr Glu Glu Ala Lys Arg Arg Ile Ala Asn Leu Lys Ile
 305 310 315 320

Gln Leu Ala Lys Leu Asp Ser Glu Ala Trp Pro Gly Val Leu Asp Ser
 325 330 335

Glu Arg Asp Arg Leu Ile Leu Ile Asn Glu Lys Glu Glu Leu Leu Lys
 340 345 350

Glu Met Arg Phe Ile Ser Pro Arg Lys Trp Thr Gln Gly Glu Val Glu
 355 360 365

Gln Leu Glu Met Ala Arg Lys Arg Leu Glu Lys Asp Leu Gln Ala Ala
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Arg Asp Thr Gln Ser Lys Ala Leu Thr Glu Arg Leu Lys Leu Asn Ser
 385 390 395 400

Lys Arg Asn Gln Leu Val Arg Glu Leu Glu Glu Ala Thr Arg Gln Val
 405 410 415

Ala Thr Leu His Ser Gln Leu Lys Ser Leu Ser Ser Ser Met Gln Ser
 420 425 430

Leu Ser Ser Gly Ser Ser Pro Gly Ser Leu Thr Ser Ser Arg Gly Ser
 435 440 445

Leu Val Ala Ser Ser Leu Asp Ser Ser Thr Ser Ala Ser Phe Thr Asp
 450 455 460

Leu Tyr Tyr Asp Pro Phe Glu Gln Leu Asp Ser Glu Leu Gln Ser Lys
 465 470 475 480

Val Glu Phe Leu Leu Leu Glu Gly Ala Thr Gly Phe Arg Pro Ser Gly
 485 490 495

Cys Ile Thr Thr Ile His Glu Asp Glu Val Ala Lys Thr Gln Lys Ala
 500 505 510

Glu Gly Gly Gly Arg Leu Gln Ala Leu Arg Ser Leu Ser Gly Thr Pro
 515 520 525

Lys Ser Met Thr Ser Leu Ser Pro Arg Ser Ser Leu Ser Ser Pro Ser
 530 535 540

Pro Pro Cys Ser Pro Leu Met Ala Asp Pro Leu Leu Ala Gly Asp Ala
 545 550 555 560

Phe Leu Asn Ser Leu Glu Phe Glu Asp Pro Glu Leu Ser Ala Thr Leu
 565 570 575

Cys Glu Leu Ser Leu Gly Asn Ser Ala Gln Glu Arg Tyr Arg Leu Glu
 580 585 590

Glu Pro Gly Thr Glu Gly Lys Gln Leu Gly Gln Ala Val Asn Thr Ala
 595 600 605

Gln Gly Cys Gly Leu Lys Val Ala Cys Val Ser Ala Ala Val Ser Asp
 610 615 620

Glu Ser Val Ala Gly Asp Ser Gly Val Tyr Glu Ala Ser Val Gln Arg
 625 630 635 640

Leu Gly Ala Ser Glu Ala Ala Ala Phe Asp Ser Asp Glu Ser Glu Ala
 645 650 655

Val Gly Ala Thr Arg Ile Gln Ile Ala Leu Lys Tyr Asp Glu Lys Asn
 660 665 670

Lys Gln Phe Ala Ile Leu Ile Ile Gln Leu Ser Asn Leu Ser Ala Leu
 675 680 685

Leu Gln Gln Gln Asp Gln Lys Val Asn Ile Arg Val Ala Val Leu Pro
 690 695 700

Cys Ser Glu Ser Thr Thr Cys Leu Phe Arg Thr Arg Pro Leu Asp Ala
 705 710 715 720
 Ser Asp Thr Leu Val Phe Asn Glu Val Phe Trp Val Ser Met Ser Tyr
 725 730 735
 Pro Ala Leu His Gln Lys Thr Leu Arg Val Asp Val Cys Thr Thr Asp
 740 745 750
 Arg Ser His Leu Glu Glu Cys Leu Gly Gly Ala Gln Ile Ser Leu Ala
 755 760 765
 Glu Val Cys Arg Ser Gly Glu Arg Ser Thr Arg Trp Tyr Asn Leu Leu
 770 775 780
 Ser Tyr Lys Tyr Leu Lys Lys Gln Ser Arg Glu Leu Lys Pro Val Gly
 785 790 795 800
 Val Met Ala Pro Ala Ser Gly Pro Ala Ser Thr Asp Ala Val Ser Ala
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 Leu Leu Glu Gln Thr Ala Val Glu Leu Glu Lys Arg Gln Glu Gly Arg
 820 825 830
 Ser Ser Thr Gln Thr Leu Glu Asp Ser Trp Arg Tyr Glu Glu Thr Ser
 835 840 845
 Glu Asn Glu Ala Val Ala Glu Glu Glu Glu Glu Val Glu Glu Glu
 850 855 860
 Glu Gly Glu Glu Asp Val Phe Thr Glu Lys Ala Ser Pro Asp Met Asp
 865 870 875 880
 Gly Tyr Pro Ala Leu Lys Val Asp Lys Glu Thr Asn Thr Glu Thr Pro
 885 890 895
 Ala Pro Ser Pro Thr Val Val Arg Pro Lys Asp Arg Arg Val Gly Thr
 900 905 910
 Pro Ser Gln Gly Pro Phe Leu Arg Gly Ser Thr Ile Ile Arg Ser Lys
 915 920 925
 Thr Phe Ser Pro Gly Pro Gln Ser Gln Tyr Val Cys Arg Leu Asn Arg
 930 935 940
 Ser Asp Ser Asp Ser Ser Thr Leu Ser Lys Lys Pro Pro Phe Val Arg
 945 950 955 960
 Asn Ser Leu Glu Arg Arg Ser Val Arg Met Lys Arg Pro Ser Ser Val
 965 970 975

Lys Ser Leu Arg Ser Glu Arg Leu Ile Arg Thr Ser Leu Asp Leu Glu
 980 985 990

Leu Asp Leu Gln Ala Thr Arg Thr Trp His Ser Gln Leu Thr Gln Glu
 995 1000 1005

Ile Ser Val Leu Lys Glu Leu Lys Glu Gln Leu Glu Gln Ala Lys
 1010 1015 1020

Ser His Gly Glu Lys Glu Leu Pro Gln Trp Leu Arg Glu Asp Glu
 1025 1030 1035

Arg Phe Arg Leu Leu Leu Arg Met Leu Glu Lys Arg Gln Met Asp
 1040 1045 1050

Arg Ala Glu His Lys Gly Glu Leu Gln Thr Asp Lys Met Met Arg
 1055 1060 1065

Ala Ala Ala Lys Asp Val His Arg Leu Arg Gly Gln Ser Cys Lys
 1070 1075 1080

Glu Pro Pro Glu Val Gln Ser Phe Arg Glu Lys Met Ala Phe Phe
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Thr Arg Pro Arg Met Asn Ile Pro Ala Leu Ser Ala Asp Asp Val
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<213> NM_001306 CLDN3, claudin 3

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<222> (198)..(857)

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gccaggccca gcgcccccg cccctcgtct ccccgacccc ggagccaccc ggtggagcgg 180

gccttgccgc ggcagcc atg tcc atg ggc ctg gag atc acg ggc acc gcg 230
 Met Ser Met Gly Leu Glu Ile Thr Gly Thr Ala

	1							5							10		
ctg gcc gtg ctg ggc tgg ctg ggc acc atc gtg tgc tgc gcg ttg ccc																	278
Leu Ala Val	15	Leu Gly Trp	Leu Gly Thr	Ile Val	Cys Cys	Ala Leu	Pro										
atg tgg cgc gtg tgc gcc ttc atc ggc agc aac atc atc acg tgc cag																	326
Met Trp Arg	30	Val Ser Ala	Phe Ile Gly	Ser Asn	Ile Ile Thr	Ser Gln											
aac atc tgg gag ggc ctg tgg atg aac tgc gtg gtg cag agc acc ggc																	374
Asn Ile Trp	45	Glu Gly Leu	Trp Met Asn	Cys Val	Val Val Gln	Ser Thr Gly											
cag atg cag tgc aag gtg tac gac tgc ctg ctg gca ctg cca cag gac																	422
Gln Met Gln	60	Cys Lys Val	Tyr Asp Ser	Leu Leu	Ala Leu	Pro Gln Asp											
ctt cag gcg gcc cgc gcc ctc atc gtg gtg gcc atc ctg ctg gcc gcc																	470
Leu Gln Ala	80	Ala Arg Ala	Leu Ile Val	Val Ala	Ile Leu	Leu Ala Ala											
ttc ggg ctg cta gtg gcg ctg gtg ggc gcc cag tgc acc aac tgc gtg																	518
Phe Gly Leu	95	Leu Val Ala	Leu Val Gly	Ala Gln	Cys Thr Asn	Cys Val											
cag gac gac acg gcc aag gcc aag atc acc atc gtg gca ggc gtg ctg																	566
Gln Asp Asp	110	Thr Ala Lys	Ala Lys Ile	Thr Ile	Val Ala	Gly Val Leu											
ttc ctt ctc gcc gcc ctg ctc acc ctc gtg ccg gtg tcc tgg tgc gcc																	614
Phe Leu Leu	125	Ala Ala Leu	Leu Leu Thr	Leu Val Pro	Val Ser Trp	Ser Ala											
aac acc att atc cgc gac ttc tac aac ccc gtg gtg ccc gag gcg cag																	662
Asn Thr Ile	140	Ile Arg Asp	Phe Tyr Asn	Pro Val	Val Pro Glu	Ala Gln											
aag cgc gag atg ggc gcg ggc ctg tac gtg ggc tgg gcg gcc gcg gcg																	710
Lys Arg Glu	160	Met Gly Ala	Gly Leu Tyr	Val Gly Trp	Ala Ala Ala	Ala Ala											
ctg cag ctg ctg ggc ggc gcg ctg ctc tgc tgc tgc tgt ccc cca cgc																	758
Leu Gln Leu	175	Leu Gly Gly	Ala Leu Leu	Cys Cys Ser	Cys Cys Pro	Pro Arg											
gag aag aag tac acg gcc acc aag gtc gtc tac tcc gcg ccg cgc tcc																	806
Glu Lys Lys	190	Tyr Thr Ala	Thr Lys Val	Val Val Tyr	Ser Ala Pro	Arg Ser											
acc ggc ccg gga gcc agc ctg ggc aca ggc tac gac cgc aag gac tac																	854
Thr Gly Pro	205	Gly Ala Ser	Leu Gly Thr	Gly Tyr Asp	Arg Lys Asp	Tyr											
gtc taagggacag acgcagggag accccaccac caccaccacc accaacacca																	907
Val	220																
ccaccaccac cgcgagctgg agcgcgcacc aggccatcca gcgtgcagcc ttgcctcgga																	967
ggccagccca cccccagaag ccaggaagcc cccgcgctgg actggggcag cttccccagc																	1027
agccacggct ttgcggggccg ggagctcgac ttgcggggccc agggaccaac ctgcatggac																	1087
tgtgaaacct cacccttctg gagcacgggg cctgggtgac cgccaatact tgaccacccc																	1147
gtcagagcccc atcggggccgc tgcccccatg ctgcgcgtgg gcagggaccg gcagccctgg																	1207

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aaaaaaaaaa aaaaaaaaaa aaaaaaa 1294

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<212> PRT

<213> NM_001306 CLDN3, claudin 3

<400> 16

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Ala Phe Ile Gly Ser Asn Ile Ile Thr Ser Gln Asn Ile Trp Glu Gly
35 40 45

Leu Trp Met Asn Cys Val Val Gln Ser Thr Gly Gln Met Gln Cys Lys
50 55 60

Val Tyr Asp Ser Leu Leu Ala Leu Pro Gln Asp Leu Gln Ala Ala Arg
65 70 75 80

Ala Leu Ile Val Val Ala Ile Leu Leu Ala Ala Phe Gly Leu Leu Val
85 90 95

Ala Leu Val Gly Ala Gln Cys Thr Asn Cys Val Gln Asp Asp Thr Ala
100 105 110

Lys Ala Lys Ile Thr Ile Val Ala Gly Val Leu Phe Leu Leu Ala Ala
115 120 125

Leu Leu Thr Leu Val Pro Val Ser Trp Ser Ala Asn Thr Ile Ile Arg
130 135 140

Asp Phe Tyr Asn Pro Val Val Pro Glu Ala Gln Lys Arg Glu Met Gly
145 150 155 160

Ala Gly Leu Tyr Val Gly Trp Ala Ala Ala Ala Leu Gln Leu Leu Gly
165 170 175

Gly Ala Leu Leu Cys Cys Ser Cys Pro Pro Arg Glu Lys Lys Tyr Thr
180 185 190

Ala Thr Lys Val Val Tyr Ser Ala Pro Arg Ser Thr Gly Pro Gly Ala
195 200 205

Ser Leu Gly Thr Gly Tyr Asp Arg Lys Asp Tyr Val
 210 215 220

<210> 17

<211> 1853

<212> DNA

<213> NM_022454 SOX17

<220>

<221> CDS

<222> (205)..(1446)

<223>

<400> 17

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ctcactcccc accccctccc ccgggtcggg ggaggcggcg cgtccggcgg aggggttgagg 180

ggagcggggc aggcctggag cgcc atg agc agc ccg gat gcg gga tac gcc 231

Met Ser Ser Pro Asp Ala Gly Tyr Ala
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agt gac gac cag agc cag acc cag agc gcg ctg ccc gcg gtg atg gcc 279

Ser Asp Asp Gln Ser Gln Thr Gln Ser Ala Leu Pro Ala Val Met Ala
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ggg ctg ggc ccc tgc ccc tgg gcc gag tgc ctg agc ccc atc ggg gac 327

Gly Leu Gly Pro Cys Pro Trp Ala Glu Ser Leu Ser Pro Ile Gly Asp
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atg aag gtg aag ggc gag gcg ccg gcg aac agc gga gca ccg gcc ggg 375

Met Lys Val Lys Gly Glu Ala Pro Ala Asn Ser Gly Ala Pro Ala Gly
 45 50 55

gcc gcg ggc cga gcc aag ggc gag tcc cgt atc cgg cgg ccg atg aac 423

Ala Ala Gly Arg Ala Lys Gly Glu Ser Arg Ile Arg Arg Pro Met Asn
 60 65 70

gct ttc atg gtg tgg gct aag gac gag cgc aag cgg ctg gcg cag cag 471

Ala Phe Met Val Trp Ala Lys Asp Glu Arg Lys Arg Leu Ala Gln Gln
 75 80 85

aat cca gac ctg cac aac gcc gag ttg agc aag atg ctg ggc aag tcg 519

Asn Pro Asp Leu His Asn Ala Glu Leu Ser Lys Met Leu Gly Lys Ser
 90 95 100 105

tgg aag gcg ctg acg ctg gcg gag aag cgg ccc ttc gtg gag gag gca 567

Trp Lys Ala Leu Thr Leu Ala Glu Lys Arg Pro Phe Val Glu Glu Ala
 110 115 120

gag cgg ctg cgc gtg cag cac atg cag gac cac ccc aac tac aag tac 615

Glu Arg Leu Arg Val Gln His Met Gln Asp His Pro Asn Tyr Lys Tyr
 125 130 135

cgg ccg cgg cgg cgc aag cag gtg aag cgg ctg aag cgg gtg gag ggc Arg Pro Arg Arg Arg Lys Gln Val Lys Arg Leu Lys Arg Val Glu Gly 140 145 150	663
ggc ttc ctg cac ggc ctg gct gag ccg cag gcg gcc gcg ctg ggc ccc Gly Phe Leu His Gly Leu Ala Glu Pro Gln Ala Ala Ala Leu Gly Pro 155 160 165	711
gag ggc ggc cgc gtg gcc atg gac ggc ctg ggc ctc cag ttc ccc gag Glu Gly Gly Arg Val Ala Met Asp Gly Leu Gly Leu Gln Phe Pro Glu 170 175 180 185	759
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cac tac cgc gac tgc cag agt ctg ggc gcg cct ccg ctc gac ggc tac His Tyr Arg Asp Cys Gln Ser Leu Gly Ala Pro Pro Leu Asp Gly Tyr 205 210 215	855
ccg ttg ccc acg ccc gac acg tcc ccg ctg gac ggc gtg gac ccc gac Pro Leu Pro Thr Pro Asp Thr Ser Pro Leu Asp Gly Val Asp Pro Asp 220 225 230	903
ccg gct ttc ttc gcc gcc ccg atg ccc ggg gac tgc ccg gcg gcc ggc Pro Ala Phe Phe Ala Ala Pro Met Pro Gly Asp Cys Pro Ala Ala Gly 235 240 245	951
acc tac agc tac gcg cag gtc tcg gac tac gct ggc ccc ccg gag cct Thr Tyr Ser Tyr Ala Gln Val Ser Asp Tyr Ala Gly Pro Pro Glu Pro 250 255 260 265	999
ccc gcc ggt ccc atg cac ccc cga ctc ggc cca gag ccc gcg ggt ccc Pro Ala Gly Pro Met His Pro Arg Leu Gly Pro Glu Pro Ala Gly Pro 270 275 280	1047
tcg att ccg ggc ctc ctg gcg cca ccc agc gcc ctt cac gtg tac tac Ser Ile Pro Gly Leu Leu Ala Pro Pro Ser Ala Leu His Val Tyr Tyr 285 290 295	1095
ggc gcg atg ggc tcg ccc ggg gcg ggc ggc ggc cgc ggc ttc cag atg Gly Ala Met Gly Ser Pro Gly Ala Gly Gly Gly Arg Gly Phe Gln Met 300 305 310	1143
cag ccg caa cac cag cac cag cac cag cac cag cac ccc ccg ggc Gln Pro Gln His Gln His Gln His Gln His Gln His His Pro Pro Gly 315 320 325	1191
ccc gga cag ccg tcg ccc cct ccg gag gca ctg ccc tgc ccg gac ggc Pro Gly Gln Pro Ser Pro Pro Pro Glu Ala Leu Pro Cys Arg Asp Gly 330 335 340 345	1239
acg gac ccc agt cag ccc gcc gag ctc ctc ggg gag gtg gac cgc acg Thr Asp Pro Ser Gln Pro Ala Glu Leu Leu Gly Glu Val Asp Arg Thr 350 355 360	1287
gaa ttt gaa cag tat ctg cac ttc gtg tgc aag cct gag atg ggc ctc Glu Phe Glu Gln Tyr Leu His Phe Val Cys Lys Pro Glu Met Gly Leu 365 370 375	1335
ccc tac cag ggg cat gac tcc ggt gtg aat ctc ccc gac agc cac ggg Pro Tyr Gln Gly His Asp Ser Gly Val Asn Leu Pro Asp Ser His Gly 380 385 390	1383
gcc att tcc tcg gtg gtg tcc gac gcc agc tcc gcg gta tat tac tgc	1431

Ala Ile Ser Ser Val Val Ser Asp Ala Ser Ser Ala Val Tyr Tyr Cys
 395 400 405
 aac tat cct gac gtg tgacagggtcc ctgattccgcc ccagcctgca ggccagaagc 1486
 Asn Tyr Pro Asp Val
 410
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<212> PRT

<213> NM_022454 SOX17

<400> 18

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Ala Glu Ser Leu Ser Pro Ile Gly Asp Met Lys Val Lys Gly Glu Ala
 35 40 45

Pro Ala Asn Ser Gly Ala Pro Ala Gly Ala Ala Gly Arg Ala Lys Gly
 50 55 60

Glu Ser Arg Ile Arg Arg Pro Met Asn Ala Phe Met Val Trp Ala Lys
 65 70 75 80

Asp Glu Arg Lys Arg Leu Ala Gln Gln Asn Pro Asp Leu His Asn Ala
 85 90 95

Glu Leu Ser Lys Met Leu Gly Lys Ser Trp Lys Ala Leu Thr Leu Ala
 100 105 110

Glu Lys Arg Pro Phe Val Glu Glu Ala Glu Arg Leu Arg Val Gln His
 115 120 125

Met Gln Asp His Pro Asn Tyr Lys Tyr Arg Pro Arg Arg Arg Lys Gln
 130 135 140

Val Lys Arg Leu Lys Arg Val Glu Gly Gly Phe Leu His Gly Leu Ala
145 150 155 160

Glu Pro Gln Ala Ala Ala Leu Gly Pro Glu Gly Gly Arg Val Ala Met
165 170 175

Asp Gly Leu Gly Leu Gln Phe Pro Glu Gln Gly Phe Pro Ala Gly Pro
180 185 190

Pro Leu Leu Pro Pro His Met Gly Gly His Tyr Arg Asp Cys Gln Ser
195 200 205

Leu Gly Ala Pro Pro Leu Asp Gly Tyr Pro Leu Pro Thr Pro Asp Thr
210 215 220

Ser Pro Leu Asp Gly Val Asp Pro Asp Pro Ala Phe Phe Ala Ala Pro
225 230 235 240

Met Pro Gly Asp Cys Pro Ala Ala Gly Thr Tyr Ser Tyr Ala Gln Val
245 250 255

Ser Asp Tyr Ala Gly Pro Pro Glu Pro Pro Ala Gly Pro Met His Pro
260 265 270

Arg Leu Gly Pro Glu Pro Ala Gly Pro Ser Ile Pro Gly Leu Leu Ala
275 280 285

Pro Pro Ser Ala Leu His Val Tyr Tyr Gly Ala Met Gly Ser Pro Gly
290 295 300

Ala Gly Gly Gly Arg Gly Phe Gln Met Gln Pro Gln His Gln His Gln
305 310 315 320

His Gln His Gln His His Pro Pro Gly Pro Gly Gln Pro Ser Pro Pro
325 330 335

Pro Glu Ala Leu Pro Cys Arg Asp Gly Thr Asp Pro Ser Gln Pro Ala
340 345 350

Glu Leu Leu Gly Glu Val Asp Arg Thr Glu Phe Glu Gln Tyr Leu His
355 360 365

Phe Val Cys Lys Pro Glu Met Gly Leu Pro Tyr Gln Gly His Asp Ser
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Gly Val Asn Leu Pro Asp Ser His Gly Ala Ile Ser Ser Val Val Ser
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<212> DNA

<213> NM_005682 GPR56

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<221> CDS

<222> (159) .. (2237)

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cagggtggtga cttccaagag tgactccgtc ggaggaaa atg act ccc cag tgc ctg	176
Met Thr Pro Gln Ser Leu	
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ctg cag acg aca ctg ttc ctg ctg agt ctg ctc ttc ctg gtc caa ggt	224
Leu Gln Thr Thr Leu Phe Leu Leu Ser Leu Leu Phe Leu Val Gln Gly	
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gcc cac ggc agg ggc cac agg gaa gac ttt cgc ttc tgc agc cag cgg	272
Ala His Gly Arg Gly His Arg Glu Asp Phe Arg Phe Cys Ser Gln Arg	
25 30 35	
aac cag aca cac agg agc agc ctc cac tac aaa ccc aca cca gac ctg	320
Asn Gln Thr His Arg Ser Ser Leu His Tyr Lys Pro Thr Pro Asp Leu	
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cgc atc tcc atc gag aac tcc gaa gag gcc ctc aca gtc cat gcc cct	368
Arg Ile Ser Ile Glu Asn Ser Glu Glu Ala Leu Thr Val His Ala Pro	
55 60 65 70	
ttc cct gca gcc cac cct gct tcc cga tcc ttc cct gac ccc agg ggc	416
Phe Pro Ala Ala His Pro Ala Ser Arg Ser Phe Pro Asp Pro Arg Gly	
75 80 85	
ctc tac cac ttc tgc ctc tac tgg aac cga cat gct ggg aga tta cat	464
Leu Tyr His Phe Cys Leu Tyr Trp Asn Arg His Ala Gly Arg Leu His	
90 95 100	
ctt ctc tat ggc aag cgt gac ttc ttg ctg agt gac aaa gcc tct agc	512
Leu Leu Tyr Gly Lys Arg Asp Phe Leu Leu Ser Asp Lys Ala Ser Ser	
105 110 115	
ctc ctc tgc ttc cag cac cag gag gag agc ctg gct cag ggc ccc ccg	560
Leu Leu Cys Phe Gln His Gln Glu Glu Ser Leu Ala Gln Gly Pro Pro	
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ctg tta gcc act tct gtc acc tcc tgg tgg agc cct cag aac atc agc	608
Leu Leu Ala Thr Ser Val Thr Ser Trp Trp Ser Pro Gln Asn Ile Ser	
135 140 145 150	
ctg ccc agt gcc gcc agc ttc acc ttc tcc ttc cac agt cct ccc cac	656

Leu Pro Ser Ala	Ala Ser Phe Thr Phe Ser Phe His Ser Pro Pro His	
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acg gcc gct cac aat gcc tcg gtg gac atg tgc gag ctc aaa agg gac	704	
Thr Ala Ala His Asn Ala Ser Val Asp Met Cys Glu Leu Lys Arg Asp		
	170 175 180	
ctc cag ctg ctc agc cag ttc ctg aag cat ccc cag aag gcc tca agg	752	
Leu Gln Leu Leu Ser Gln Phe Leu Lys His Pro Gln Lys Ala Ser Arg		
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agg ccc tcg gct gcc ccc gcc agc cag cag ttg cag agc ctg gag tcg	800	
Arg Pro Ser Ala Ala Pro Ala Ser Gln Gln Leu Gln Ser Leu Glu Ser		
	200 205 210	
aaa ctg acc tct gtg aga ttc atg ggg gac atg gtg tcc ttc gag gag	848	
Lys Leu Thr Ser Val Arg Phe Met Gly Asp Met Val Ser Phe Glu Glu		
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gac cgg atc aac gcc acg gtg tgg aag ctc cag ccc aca gcc ggc ctc	896	
Asp Arg Ile Asn Ala Thr Val Trp Lys Leu Gln Pro Thr Ala Gly Leu		
	235 240 245	
cag gac ctg cac atc cac tcc cgg cag gag gag gag cag agc gag atc	944	
Gln Asp Leu His Ile His Ser Arg Gln Glu Glu Gln Ser Glu Ile		
	250 255 260	
atg gag tac tcg gtg ctg ctg cct cga aca ctc ttc cag agg acg aaa	992	
Met Glu Tyr Ser Val Leu Leu Pro Arg Thr Leu Phe Gln Arg Thr Lys		
	265 270 275	
ggc cgg agc ggg gag gct gag aag aga ctc ctc ctg gtg gac ttc agc	1040	
Gly Arg Ser Gly Glu Ala Glu Lys Arg Leu Leu Val Asp Phe Ser		
	280 285 290	
agc caa gcc ctg ttc cag gac aag aat tcc agc cac gtc ctg ggt gag	1088	
Ser Gln Ala Leu Phe Gln Asp Lys Asn Ser Ser His Val Leu Gly Glu		
	295 300 305 310	
aag gtc ttg ggg att gtg gta cag aac acc aaa gta gcc aac ctc acg	1136	
Lys Val Leu Gly Ile Val Val Gln Asn Thr Lys Val Ala Asn Leu Thr		
	315 320 325	
gag ccc gtg gtg ctc acc ttc cag cac cag cta cag ccg aag aat gtg	1184	
Glu Pro Val Val Leu Thr Phe Gln His Gln Leu Gln Pro Lys Asn Val		
	330 335 340	
act ctg caa tgt gtg ttc tgg gtt gaa gac ccc aca ttg agc agc ccg	1232	
Thr Leu Gln Cys Val Phe Trp Val Glu Asp Pro Thr Leu Ser Ser Pro		
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ggg cat tgg agc agt gct ggg tgt gag acc gtc agg aga gaa acc caa	1280	
Gly His Trp Ser Ser Ala Gly Cys Glu Thr Val Arg Arg Glu Thr Gln		
	360 365 370	
aca tcc tgc ttc tgc aac cac ttg acc tac ttt gca gtg ctg atg gtc	1328	
Thr Ser Cys Phe Cys Asn His Leu Thr Tyr Phe Ala Val Leu Met Val		
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Ser Tyr Val Gly Cys Val Val Ser Ala Leu Ala Cys Leu Val Thr Ile		
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<212> PRT

<213> NM_005682 GPR56

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 325 330 335
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 340 345 350
 Pro Thr Leu Ser Ser Pro Gly His Trp Ser Ser Ala Gly Cys Glu Thr
 355 360 365
 Val Arg Arg Glu Thr Gln Thr Ser Cys Phe Cys Asn His Leu Thr Tyr
 370 375 380
 Phe Ala Val Leu Met Val Ser Ser Val Glu Val Asp Ala Val His Lys
 385 390 395 400
 His Tyr Leu Ser Leu Leu Ser Tyr Val Gly Cys Val Val Ser Ala Leu
 405 410 415
 Ala Cys Leu Val Thr Ile Ala Ala Tyr Leu Cys Ser Arg Val Pro Leu
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 Pro Cys Arg Arg Lys Pro Arg Asp Tyr Thr Ile Lys Val His Met Asn
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 Leu Leu Leu Ala Val Phe Leu Leu Asp Thr Ser Phe Leu Leu Ser Glu
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 Pro Val Ala Leu Thr Gly Ser Glu Ala Gly Cys Arg Ala Ser Ala Ile
 465 470 475 480
 Phe Leu His Phe Ser Leu Leu Thr Cys Leu Ser Trp Met Gly Leu Glu
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 Gly Tyr Asn Leu Tyr Arg Leu Val Val Glu Val Phe Gly Thr Tyr Val
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 Pro Gly Tyr Leu Leu Lys Leu Ser Ala Met Gly Trp Gly Phe Pro Ile
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 Phe Leu Val Thr Leu Val Ala Leu Val Asp Val Asp Asn Tyr Gly Pro
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 Ile Ile Leu Ala Val His Arg Thr Pro Glu Gly Val Ile Tyr Pro Ser
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Met Cys Trp Ile Arg Asp Ser Leu Val Ser Tyr Ile Thr Asn Leu Gly
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Leu Phe Ser Leu Val Phe Leu Phe Asn Met Ala Met Leu Ala Thr Met
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Val Val Gln Ile Leu Arg Leu Arg Pro His Thr Gln Lys Trp Ser His
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Val Leu Thr Leu Leu Gly Leu Ser Leu Val Leu Gly Leu Pro Trp Ala
610 615 620

Leu Ile Phe Phe Ser Phe Ala Ser Gly Thr Phe Gln Leu Val Val Leu
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Tyr Leu Phe Ser Ile Ile Thr Ser Phe Gln Gly Phe Leu Ile Phe Ile
645 650 655

Trp Tyr Trp Ser Met Arg Leu Gln Ala Arg Gly Gly Pro Ser Pro Leu
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Ser Ser Ser Arg Ile
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 Leu Leu Gly Trp Val Gly Leu Val Ala Cys Thr Ala Ile Pro Gln Trp
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 cag atg agc tcc tat gcg ggt gac aac atc atc acg gcc cag gcc atg 564
 Gln Met Ser Ser Tyr Ala Gly Asp Asn Ile Ile Thr Ala Gln Ala Met
 35 40 45
 tac aag ggg ctg tgg atg gac tgc gtc acg cag agc acg ggg atg atg 612
 Tyr Lys Gly Leu Trp Met Asp Cys Val Thr Gln Ser Thr Gly Met Met
 50 55 60
 agc tgc aaa atg tac gac tcg gtg ctc gcc ctg tcc gcg gcc ttg cag 660
 Ser Cys Lys Met Tyr Asp Ser Val Leu Ala Leu Ser Ala Ala Leu Gln
 65 70 75
 gcc act cga gcc cta atg gtg gtc tcc ctg gtg ctg ggc ttc ctg gcc 708
 Ala Thr Arg Ala Leu Met Val Val Ser Leu Val Leu Gly Phe Leu Ala
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 atg ttt gtg gcc acg atg ggc atg aag tgc acg cgc tgt ggg gga gac 756
 Met Phe Val Ala Thr Met Gly Met Lys Cys Thr Arg Cys Gly Gly Asp
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 gac aaa gtg aag aag gcc cgt ata gcc atg ggt gga ggc ata att ttc 804
 Asp Lys Val Lys Lys Ala Arg Ile Ala Met Gly Gly Gly Ile Ile Phe
 115 120 125
 atc gtg gca ggt ctt gcc acc ttg gta gct tgc tcc tgg tat ggc cat 852
 Ile Val Ala Gly Leu Ala Thr Leu Val Ala Cys Ser Trp Tyr Gly His
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 cag att gtc aca gac ttt tat aac cct ttg atc cct acc aac att aag 900
 Gln Ile Val Thr Asp Phe Tyr Asn Pro Leu Ile Pro Thr Asn Ile Lys
 145 150 155
 tat gag ttt ggc cct gcc atc ttt att ggc tgg gca ggg tct gcc cta 948
 Tyr Glu Phe Gly Pro Ala Ile Phe Ile Gly Trp Ala Gly Ser Ala Leu
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 gtc atc ctg gga ggt gca ctg ctc tcc tgt tcc tgt cct ggg aat gag 996
 Val Ile Leu Gly Gly Ala Leu Leu Ser Cys Ser Cys Pro Gly Asn Glu
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 agc aag gct ggg tac cgt gca ccc cgc tct tac cct aag tcc aac tct 1044
 Ser Lys Ala Gly Tyr Arg Ala Pro Arg Ser Tyr Pro Lys Ser Asn Ser
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<213> NM_001307 claudin 7, CLDN7

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Ser Ser Tyr Ala Gly Asp Asn Ile Ile Thr Ala Gln Ala Met Tyr Lys
 35 40 45

Gly Leu Trp Met Asp Cys Val Thr Gln Ser Thr Gly Met Met Ser Cys
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Lys Met Tyr Asp Ser Val Leu Ala Leu Ser Ala Ala Leu Gln Ala Thr
 65 70 75 80

Arg Ala Leu Met Val Val Ser Leu Val Leu Gly Phe Leu Ala Met Phe
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Val Ala Thr Met Gly Met Lys Cys Thr Arg Cys Gly Gly Asp Asp Lys
 100 105 110

Val Lys Lys Ala Arg Ile Ala Met Gly Gly Gly Ile Ile Phe Ile Val
 115 120 125

Ala Gly Leu Ala Thr Leu Val Ala Cys Ser Trp Tyr Gly His Gln Ile
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Val Thr Asp Phe Tyr Asn Pro Leu Ile Pro Thr Asn Ile Lys Tyr Glu
 145 150 155 160

Phe Gly Pro Ala Ile Phe Ile Gly Trp Ala Gly Ser Ala Leu Val Ile
 165 170 175

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Glu Tyr Val
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<222> (75)..(407)

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Tyr Arg Lys Val Val Ala Ala Arg Ala Pro Arg Lys Val Leu Gly Ser
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tcc acc tct gcc act aat tcg aca tca gtt tca tcg agg aaa gct gaa      206
Ser Thr Ser Ala Thr Asn Ser Thr Ser Val Ser Ser Arg Lys Ala Glu
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aat aaa tat gca gga ggg aac ccc gtt tgc gtg cgc cca act ccc aag      254
Asn Lys Tyr Ala Gly Gly Asn Pro Val Cys Val Arg Pro Thr Pro Lys
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Glu Lys Glu Asn Gln Ile Pro Glu Glu Ala Gly Ser Ser Gly Leu Gly
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aaa gca aag aga aaa gca tgt cct ttg caa cct gat cac aca aat gat      398
Lys Ala Lys Arg Lys Ala Cys Pro Leu Gln Pro Asp His Thr Asn Asp
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gaa aaa gaa tagaactttc tcattcatct ttgaataacg tctccttggt      447
Glu Lys Glu
          110

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aacaggcatt taattaaata atttaggttt aaatttagat gttcaaaagt agttgtgaaa      567
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58

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<212> PRT

<213> NM_014736 KIAA0101 gene product

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Thr Asn Ser Thr Ser Val Ser Ser Arg Lys Ala Glu Asn Lys Tyr Ala
35 40 45

Gly Gly Asn Pro Val Cys Val Arg Pro Thr Pro Lys Trp Gln Lys Gly
50 55 60

Ile Gly Glu Phe Phe Arg Leu Ser Pro Lys Asp Ser Glu Lys Glu Asn
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<222> (23)..(418)

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52

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Val Leu Leu Ala Leu Gly Thr Leu Ala Pro Trp Ala Val Glu Gly Ser
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Gly Lys Ser Phe Lys Ala Gly Val Cys Pro Pro Lys Lys Ser Ala Gln
30 35 40

tgc ctt aga tac aag aaa cct gag tgc cag agt gac tgg cag tgt cca 196
Cys Leu Arg Tyr Lys Lys Pro Glu Cys Gln Ser Asp Trp Gln Cys Pro
45 50 55

ggg aag aag aga tgt tgt cct gac act tgt ggc atc aaa tgc ctg gat 244
Gly Lys Lys Arg Cys Cys Pro Asp Thr Cys Gly Ile Lys Cys Leu Asp
60 65 70

cct gtt gac acc cca aac cca aca agg agg aag cct ggg aag tgc cca 292
Pro Val Asp Thr Pro Asn Pro Thr Arg Arg Lys Pro Gly Lys Cys Pro
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gtg act tat ggc caa tgt ttg atg ctt aac ccc ccc aat ttc tgt gag 340
Val Thr Tyr Gly Gln Cys Leu Met Leu Asn Pro Pro Asn Phe Cys Glu
95 100 105

atg gat ggc cag tgc aag cgt gac ttg aag tgt tgc atg ggc atg tgt 388
Met Asp Gly Gln Cys Lys Arg Asp Leu Lys Cys Cys Met Gly Met Cys
110 115 120

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Gly Lys Ser Cys Val Ser Pro Val Lys Ala
125 130

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cactgatatc ctcccttggg gaaaggcttg gcacacagca ggctttcaag aagtgccagt 558

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<211> 132

<212> PRT

<213> NM_003064 secretory leukocyte protease inhibitor, SLPI

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35 40 45

Pro Glu Cys Gln Ser Asp Trp Gln Cys Pro Gly Lys Lys Arg Cys Cys
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Pro Asp Thr Cys Gly Ile Lys Cys Leu Asp Pro Val Asp Thr Pro Asn
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Pro Thr Arg Arg Lys Pro Gly Lys Cys Pro Val Thr Tyr Gly Gln Cys
85 90 95

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<212> DNA

<213> NM_013994 DDR1

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Met Gly Pro Glu Ala Leu
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Ser Ser Leu Leu Leu Leu Leu Val Ala Ser Gly Asp Ala Asp Met
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Lys Gly His Phe Asp Pro Ala Lys Cys Arg Tyr Ala Leu Gly Met Gln
25 30 35
gac cgg acc atc cca gac agt gac atc tct gct tcc agc tcc tgg tca 498
Asp Arg Thr Ile Pro Asp Ser Asp Ile Ser Ala Ser Ser Ser Trp Ser
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Gly	Ala	Trp	Cys	Pro	Ala	Gly	Ser	Val	Phe	Pro	Lys	Glu	Glu	Glu	Tyr	
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Leu	Gln	Val	Asp	Leu	Gln	Arg	Leu	His	Leu	Val	Ala	Leu	Val	Gly	Thr	
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Gln	Gly	Arg	His	Ala	Gly	Gly	Leu	Gly	Lys	Glu	Phe	Ser	Arg	Ser	Tyr	
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Arg	Leu	Arg	Tyr	Ser	Arg	Asp	Gly	Arg	Arg	Trp	Met	Gly	Trp	Lys	Asp	
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Tyr	Pro	Arg	Ala	Asp	Arg	Val	Met	Ser	Val	Cys	Leu	Arg	Val	Glu	Leu	
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Gly	Gln	Thr	Met	Tyr	Leu	Ser	Glu	Ala	Val	Tyr	Leu	Asn	Asp	Ser	Thr	
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Leu	Arg	Val	Trp	Pro	Gly	Tyr	Asp	Tyr	Val	Gly	Trp	Ser	Asn	His	Ser	
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Phe	Ser	Ser	Gly	Tyr	Val	Glu	Met	Glu	Phe	Glu	Phe	Asp	Arg	Leu	Arg	
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Ala	Phe	Gln	Ala	Met	Gln	Val	His	Cys	Asn	Asn	Met	His	Thr	Leu	Gly	
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gcc	cgt	ctg	cct	ggc	ggg	gtg	gaa	tgt	cgc	ttc	cgg	cgt	ggc	cct	gcc	1266
Ala	Arg	Leu	Pro	Gly	Gly	Val	Glu	Cys	Arg	Phe	Arg	Arg	Gly	Pro	Ala	
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atg	gcc	tgg	gag	ggg	gag	ccc	atg	cgc	cac	aac	cta	ggg	ggc	aac	ctg	1314
Met	Ala	Trp	Glu	Gly	Glu	Pro	Met	Arg	His	Asn	Leu	Gly	Gly	Asn	Leu	
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gcc aaa ccc acc aac acc cag gcc tac agt ggg gac tat atg gag cct Ala Lys Pro Thr Asn Thr Gln Ala Tyr Ser Gly Asp Tyr Met Glu Pro 535 540 545 550	1986
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840 845 850

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Val Ala Leu Val Gly Thr Gln Gly Arg His Ala Gly Gly Leu Gly Lys		
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Glu Phe Ser Arg Ser Tyr Arg Leu Arg Tyr Ser Arg Asp Gly Arg Arg		
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Trp Met Gly Trp Lys Asp Arg Trp Gly Gln Glu Val Ile Ser Gly Asn		
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Glu Asp Pro Glu Gly Val Val Leu Lys Asp Leu Gly Pro Pro Met Val		
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Ala Arg Leu Val Arg Phe Tyr Pro Arg Ala Asp Arg Val Met Ser Val		
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Cys Leu Arg Val Glu Leu Tyr Gly Cys Leu Trp Arg Asp Gly Leu Leu		
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Ser Tyr Thr Ala Pro Val Gly Gln Thr Met Tyr Leu Ser Glu Ala Val		
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Tyr Leu Asn Asp Ser Thr Tyr Asp Gly His Thr Val Gly Gly Leu Gln		
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Phe Arg Lys Ser Gln Glu Leu Arg Val Trp Pro Gly Tyr Asp Tyr Val		
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Gly Trp Ser Asn His Ser Phe Ser Ser Gly Tyr Val Glu Met Glu Phe		
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Asn Met His Thr Leu Gly Ala Arg Leu Pro Gly Gly Val Glu Cys Arg		

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 Phe Arg Arg Gly Pro Ala Met Ala Trp Glu Gly Glu Pro Met Arg His
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 370 375 380
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 Ile Ile Ala Leu Met Leu Trp Arg Leu His Trp Arg Arg Leu Leu Ser
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 Lys Ala Glu Arg Arg Val Leu Glu Glu Glu Leu Thr Val His Leu Ser
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 Gly Asp Tyr Met Glu Pro Glu Lys Pro Gly Ala Pro Leu Leu Pro Pro
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Pro Pro Gln Asn Ser Val Pro His Tyr Ala Glu Ala Asp Ile Val Thr
565 570 575

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Pro Gly Ala Val Gly Asp Gly Pro Pro Arg Val Asp Phe Pro Arg Ser
595 600 605

Arg Leu Arg Phe Lys Glu Lys Leu Gly Glu Gly Gln Phe Gly Glu Val
610 615 620

His Leu Cys Glu Val Asp Ser Pro Gln Asp Leu Val Ser Leu Asp Phe
625 630 635 640

Pro Leu Asn Val Arg Lys Gly His Pro Leu Leu Val Ala Val Lys Ile
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Leu Arg Pro Asp Ala Thr Lys Asn Ala Ser Phe Ser Leu Phe Ser Arg
660 665 670

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Asn Ile Ile Arg Leu Leu Gly Val Cys Val Gln Asp Asp Pro Leu Cys
690 695 700

Met Ile Thr Asp Tyr Met Glu Asn Gly Asp Leu Asn Gln Phe Leu Ser
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Ala His Gln Leu Glu Asp Lys Ala Ala Glu Gly Ala Pro Gly Asp Gly
725 730 735

Gln Ala Ala Gln Gly Pro Thr Ile Ser Tyr Pro Met Leu Leu His Val
740 745 750

Ala Ala Gln Ile Ala Ser Gly Met Arg Tyr Leu Ala Thr Leu Asn Phe
755 760 765

Val His Arg Asp Leu Ala Thr Arg Asn Cys Leu Val Gly Glu Asn Phe
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Thr Ile Lys Ile Ala Asp Phe Gly Met Ser Arg Asn Leu Tyr Ala Gly
785 790 795 800

Asp Tyr Tyr Arg Val Gln Gly Arg Ala Val Leu Pro Ile Arg Trp Met
805 810 815

Ala Trp Glu Cys Ile Leu Met Gly Lys Phe Thr Thr Ala Ser Asp Val
820 825 830

Trp Ala Phe Gly Val Thr Leu Trp Glu Val Leu Met Leu Cys Arg Ala
835 840 845

Gln Pro Phe Gly Ser Ala His Arg Arg Ala Gly His Arg Glu Arg Gly
850 855 860

Gly Val Leu Pro Gly Pro Gly Pro Ala Val Tyr Leu Ser Arg Pro Pro
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Ala Cys Pro Gln Gly Leu Tyr Glu Leu Met Leu Arg Cys Trp Ser Arg
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Met Glu Val Ser Pro Leu Gln Pro Val Asn Glu Asn Met Gln
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Glu Arg Ile Tyr Gln Lys Lys Thr Gln Leu Glu His Ile Leu Leu Arg
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Pro Asp Thr Tyr Ile Gly Ser Val Glu Leu Val Thr Gln Gln Met Trp
50 55 60
gtt tac gat gaa gat gtt ggc att aac tat agg gaa gtc act ttt gtt 360

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Pro Gly Leu Tyr Lys Ile Phe Asp Glu Ile Leu Val Asn Ala Ala Asp	
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Asn Lys Gln Arg Asp Pro Lys Met Ser Cys Ile Arg Val Thr Ile Asp	
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Pro Glu Asn Asn Leu Ile Ser Ile Trp Asn Asn Gly Lys Gly Ile Pro	
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Met Val Arg Arg Ala Tyr Asp Ile Ala Gly Ser Thr Lys Asp Val Lys	
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Lys	Arg	Asn	Asp	Lys	Arg	Glu	Val	Lys	Val	Ala	Gln	Leu	Ala	Gly	Ser	
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Val	Ala	Glu	Met	Ser	Ser	Tyr	His	His	Gly	Glu	Met	Ser	Leu	Met	Met	
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Thr	Ile	Ile	Asn	Leu	Ala	Gln	Asn	Phe	Val	Gly	Ser	Asn	Asn	Leu	Asn	
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ctc	ttg	cag	ccc	att	ggg	cag	ttt	ggg	acc	agg	cta	cat	ggg	ggc	aag	2520
Leu	Leu	Gln	Pro	Ile	Gly	Gln	Phe	Gly	Thr	Arg	Leu	His	Gly	Gly	Lys	
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Asp	Ser	Ala	Ser	Pro	Arg	Tyr	Ile	Phe	Thr	Met	Leu	Ser	Ser			

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Thr Leu Lys Arg Lys Ser Pro Ser Asp Leu Trp Lys Glu Asp Leu	
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Asn Phe Asp Val Pro Pro Arg Glu Thr Glu Pro Arg Arg Ala Ala	
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Thr Ser Thr Thr Gly Ala Lys Lys Arg	Ala Ala Pro Lys Gly Thr	
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Thr Ser Lys Lys Ser Lys Gly Glu Ser	Asp Asp Phe His Met Asp	
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 35 40 45

Thr Tyr Ile Gly Ser Val Glu Leu Val Thr Gln Gln Met Trp Val Tyr
 50 55 60

Asp Glu Asp Val Gly Ile Asn Tyr Arg Glu Val Thr Phe Val Pro Gly
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Leu Tyr Lys Ile Phe Asp Glu Ile Leu Val Asn Ala Ala Asp Asn Lys
 85 90 95

Gln Arg Asp Pro Lys Met Ser Cys Ile Arg Val Thr Ile Asp Pro Glu
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Asn Asn Leu Ile Ser Ile Trp Asn Asn Gly Lys Gly Ile Pro Val Val
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Glu His Lys Val Glu Lys Met Tyr Val Pro Ala Leu Ile Phe Gly Gln
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Lys Gly Gly Arg His Val Asp Tyr Val Ala Asp Gln Ile Val Thr Lys
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Ala His Gln Val Lys Asn His Met Trp Ile Phe Val Asn Ala Leu Ile
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Glu Asn Pro Thr Phe Asp Ser Gln Thr Lys Glu Asn Met Thr Leu Gln
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Pro Lys Ser Phe Gly Ser Thr Cys Gln Leu Ser Glu Lys Phe Ile Lys
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Ala Ala Ile Gly Cys Gly Ile Val Glu Ser Ile Leu Asn Trp Val Lys
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Gly Arg Asn Ser Thr Glu Cys Thr Leu Ile Leu Thr Glu Gly Asp Ser
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Ala Lys Thr Leu Ala Val Ser Gly Leu Gly Val Val Gly Arg Asp Lys
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Tyr Gly Val Phe Pro Leu Arg Gly Lys Ile Leu Asn Val Arg Glu Ala
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Ser His Lys Gln Ile Met Glu Asn Ala Glu Ile Asn Asn Ile Ile Lys
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Lys Thr Leu Arg Tyr Gly Lys Ile Met Ile Met Thr Asp Gln Asp Gln
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Asp Gly Ser His Ile Lys Gly Leu Leu Ile Asn Phe Ile His His Asn
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Trp Pro Ser Leu Leu Arg His Arg Phe Leu Glu Glu Phe Ile Thr Pro
565 570 575

Ile Val Lys Val Ser Lys Asn Lys Gln Glu Met Ala Phe Tyr Ser Leu
580 585 590

Pro Glu Phe Glu Glu Trp Lys Ser Ser Thr Pro Asn His Lys Lys Trp
595 600 605

Lys Val Lys Tyr Tyr Lys Gly Leu Gly Thr Ser Thr Ser Lys Glu Ala
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Lys Glu Tyr Phe Ala Asp Met Lys Arg His Arg Ile Gln Phe Lys Tyr
625 630 635 640

Ser Gly Pro Glu Asp Asp Ala Ala Ile Ser Leu Ala Phe Ser Lys Lys
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Gln Ile Asp Asp Arg Lys Glu Trp Leu Thr Asn Phe Met Glu Asp Arg
660 665 670

Arg Gln Arg Lys Leu Leu Gly Leu Pro Glu Asp Tyr Leu Tyr Gly Gln
675 680 685

Thr Thr Thr Tyr Leu Thr Tyr Asn Asp Phe Ile Asn Lys Glu Leu Ile
690 695 700

Leu Phe Ser Asn Ser Asp Asn Glu Arg Ser Ile Pro Ser Met Val Asp

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 740 745 750
 Glu Met Ser Ser Tyr His His Gly Glu Met Ser Leu Met Met Thr Ile
 755 760 765
 Ile Asn Leu Ala Gln Asn Phe Val Gly Ser Asn Asn Leu Asn Leu Leu
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 785 790 795 800
 Ala Ser Pro Arg Tyr Ile Phe Thr Met Leu Ser Ser Leu Ala Arg Leu
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 Asn Gln Arg Val Glu Pro Glu Trp Tyr Ile Pro Ile Ile Pro Met Val
 835 840 845
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 Pro Asn Phe Asp Val Arg Glu Ile Val Asn Asn Ile Arg Arg Leu Met
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 Asp Gly Glu Glu Pro Leu Pro Met Leu Pro Ser Tyr Lys Asn Phe Lys
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 Gly Thr Ile Glu Glu Leu Ala Pro Asn Gln Tyr Val Ile Ser Gly Glu
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 Val Ala Ile Leu Asn Ser Thr Thr Ile Glu Ile Ser Glu Leu Pro Val
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 Arg Thr Trp Thr Gln Thr Tyr Lys Glu Gln Val Leu Glu Pro Met Leu
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 Asn Gly Thr Glu Lys Thr Pro Pro Leu Ile Thr Asp Tyr Arg Glu Tyr
 945 950 955 960
 His Thr Asp Thr Thr Val Lys Phe Val Val Lys Met Thr Glu Glu Lys
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980 985 990
 Thr Ser Leu Thr Cys Asn Ser Met Val Leu Phe Asp His Val Gly Cys
 995 1000 1005

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 Gly Met Leu Gly Ala Glu Ser Ala Lys Leu Asn Asn Gln Ala Arg
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 Phe Ile Leu Glu Lys Ile Asp Gly Lys Ile Ile Ile Glu Asn Lys
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 Pro Lys Lys Glu Leu Ile Lys Val Leu Ile Gln Arg Gly Tyr Asp
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 Ser Asp Pro Val Lys Ala Trp Lys Glu Ala Gln Gln Lys Val Pro
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 1160 1165 1170

 Phe Ile Glu Glu Leu Glu Ala Val Glu Ala Lys Glu Lys Gln Asp
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 Glu Gln Val Gly Leu Pro Gly Lys Gly Gly Lys Ala Lys Gly Lys
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 Lys Thr Gln Met Ala Glu Val Leu Pro Ser Pro Arg Gly Gln Arg
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 Lys Asn Lys Lys Lys Ile Lys Asn Glu Asn Thr Glu Gly Ser Pro

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Thr Leu Ala Phe Lys Pro Ile	Lys Lys Gly Lys Lys Arg Asn Pro	
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Trp Ser Asp Ser Glu Ser Asp	Arg Ser Ser Asp Glu Ser Asn Phe	
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Asp Val Pro Pro Arg Glu Thr	Glu Pro Arg Arg Ala Ala Thr Lys	
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Thr Lys Phe Thr Met Asp Leu	Asp Ser Asp Glu Asp Phe Ser Asp	
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Phe Asp Glu Lys Thr Asp Asp	Glu Asp Phe Val Pro Ser Asp Ala	
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Ser Pro Pro Lys Thr Lys Thr	Ser Pro Lys Leu Ser Asn Lys Glu	
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ctc gga ccc ggg gcc ggc gcg gcc cag ccc agc gcg agc ccc ttg gag      335
Leu Gly Pro Gly Ala Gly Ala Ala Gln Pro Ser Ala Ser Pro Leu Glu
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ggg ctg ctg gac ctc agc tac ccc cgc acc cac gcg gcc ctg ctg aaa      383
Gly Leu Leu Asp Leu Ser Tyr Pro Arg Thr His Ala Ala Leu Leu Lys
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Val Ala Gln Met Val Thr Leu Leu Ile Ala Phe Ile Cys Val Arg Ser
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tcc ctg tgg acc aac tac agc gcc tac agc tac ttt gaa gtg gtc acc      479
Ser Leu Trp Thr Asn Tyr Ser Ala Tyr Ser Tyr Phe Glu Val Val Thr
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Ile Cys Asp Leu Ile Met Ile Leu Ala Phe Tyr Leu Val His Leu Phe
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cgc ttc tac cgc gtg ctc acc tgt atc agc tgg ccc ctg tcg gaa ctt      575

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Ala Ala Ser Lys Ser Tyr Asn Gln Ser Gly Leu Val Ala Gly Ala Ile
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Phe Gly Phe Met Ala Thr Phe Leu Cys Met Ala Ser Ile Trp Leu Ser
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Tyr Lys Ile Ser Cys Val Thr Gln Ser Thr Asp Ala Ala Val
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Glu Gly Leu Leu Asp Leu Ser Tyr Pro Arg Thr His Ala Ala Leu Leu
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Lys Val Ala Gln Met Val Thr Leu Leu Ile Ala Phe Ile Cys Val Arg
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Ser Ser Leu Trp Thr Asn Tyr Ser Ala Tyr Ser Tyr Phe Glu Val Val
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Phe Arg Phe Tyr Arg Val Leu Thr Cys Ile Ser Trp Pro Leu Ser Glu
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Leu Leu His Tyr Leu Ile Gly Thr Leu Leu Leu Leu Ile Ala Ser Ile
115 120 125

Val Ala Ala Ser Lys Ser Tyr Asn Gln Ser Gly Leu Val Ala Gly Ala
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Met Ser Gln Val Lys Ser
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Asn Gly Thr Gly Gly Leu Phe Gln Gly Lys Thr Pro Leu Arg Lys Ala
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Asn Leu Gln Gln Ala Ile Val Thr Pro Leu Lys Pro Val Asp Asn Thr
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Tyr Tyr Lys Glu Ala Glu Lys Glu Asn Leu Val Glu Gln Ser Ile Pro
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Ser Asn Ala Cys Ser Ser Leu Glu Val Glu Ala Ala Ile Ser Arg Lys
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Thr Pro Ala Gln Pro Gln Arg Arg Ser Leu Arg Leu Ser Ala Gln Lys
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Asp Leu Glu Gln Lys Glu Lys His His Val Lys Met Lys Ala Lys Arg
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Cys Ala Thr Pro Val Ile Ile Asp Glu Ile Leu Pro Ser Lys Lys Met
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Lys Val Ser Asn Asn Lys Lys Lys Pro Glu Glu Glu Gly Ser Ala His
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Gln Asp Thr Ala Glu Lys Asn Ala Ser Ser Pro Glu Lys Ala Lys Gly
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Arg His Thr Val Pro Cys Met Pro Pro Ala Lys Gln Lys Phe Leu Lys
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Ser Thr Glu Glu Gln Glu Leu Glu Lys Ser Met Lys Met Gln Gln Glu
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Ser Val Asp Phe His Phe Arg Thr Asp Glu Arg Ile Lys Gln His Pro
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Val Ser Thr Tyr Val Pro Leu Ala Gln Gln Val Glu Asp Phe His Lys
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Arg Thr Pro Asn Arg Tyr His Leu Arg Ser Lys Lys Asp Asp Ile Asn
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Leu Leu Pro Ser Lys Ser Ser Val Thr Lys Ile Cys Arg Asp Pro Gln
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Thr Pro Val Leu Gln Thr Lys His Arg Ala Arg Ala Val Thr Cys Lys
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Ser Thr Ala Glu Leu Glu Ala Glu Glu Leu Glu Lys Leu Gln Gln Tyr
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Lys Phe Lys Ala Arg Glu Leu Asp Pro Arg Ile Leu Glu Gly Gly Pro
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Ile Leu Pro Lys Lys Pro Pro Val Lys Pro Pro Thr Glu Pro Ile Gly
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Phe Asp Leu Glu Ile Glu Lys Arg Ile Gln Glu Arg Glu Ser Lys Lys
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Lys Thr Glu Asp Glu His Phe Glu Phe His Ser Arg Pro Cys Pro Thr
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Ile Thr Val Pro Lys Ser Pro Ala Phe Ala Leu Lys Asn Arg Ile Arg
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Met Pro Thr Lys Glu Asp Glu Glu Glu Asp Glu Pro Val Val Ile Lys
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Ala Gln Pro Val Pro His Tyr Gly Val Pro Phe Lys Pro Gln Ile Pro
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Gly Glu Val Pro Lys Phe Lys Ala Leu Pro Leu Pro His Phe Asp Thr
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Lys His Gln Leu Glu Glu Glu Leu Arg Gln Gln Lys Glu Ala Ala Cys
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Phe Lys Ala Arg Pro Asn Thr Val Ile Ser Gln Glu Pro Phe Val Pro
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Lys Lys Glu Lys Lys Ser Val Ala Glu Gly Leu Ser Gly Ser Leu Val
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Gln Glu Pro Phe Gln Leu Ala Thr Glu Lys Arg Ala Lys Glu Arg Gln
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Glu Leu Glu Lys Arg Met Ala Glu Val Glu Ala Gln Lys Ala Gln Gln
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Leu Glu Glu Ala Arg Leu Gln Glu Glu Glu Gln Lys Lys Glu Glu Leu
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Ala Arg Leu Arg Arg Glu Leu Val His Lys Ala Asn Pro Ile Arg Lys
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ttc atc ttc tgg ctt gcc ggg att gct gtc ctt gcc att gga cta tgg 213
 Phe Ile Phe Trp Leu Ala Gly Ile Ala Val Leu Ala Ile Gly Leu Trp
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ctc cga ttc gac tct cag acc aag agc atc ttc gag caa gaa act aat 261
 Leu Arg Phe Asp Ser Gln Thr Lys Ser Ile Phe Glu Gln Glu Thr Asn
 35 40 45 50

aat aat aat tcc agc ttc tac aca gga gtc tat att ctg atc gga gcc 309
 Asn Asn Asn Ser Ser Phe Tyr Thr Gly Val Tyr Ile Leu Ile Gly Ala
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 Gly Ala Leu Met Met Leu Val Gly Phe Leu Gly Cys Cys Gly Ala Val
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cag gag tcc cag tgc atg ctg gga ctg ttc ttc ggc ttc ctc ttg gtg 405
 Gln Glu Ser Gln Cys Met Leu Gly Leu Phe Phe Gly Phe Leu Leu Val
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 Ile Phe Ala Ile Glu Ile Ala Ala Ala Ile Trp Gly Tyr Ser His Lys
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gat gag gtg att aag gaa gtc cag gag ttt tac aag gac acc tac aac 501
 Asp Glu Val Ile Lys Glu Val Gln Glu Phe Tyr Lys Asp Thr Tyr Asn
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aag ctg aaa acc aag gat gag ccc cag cgg gaa acg ctg aaa gcc atc 549

Lys Leu Lys Thr Lys Asp Glu Pro Gln Arg Glu Thr Leu Lys Ala Ile
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 Lys Ser Cys Pro Asp Ala Ile Lys Glu Val Phe Asp Asn Lys Phe His
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Gly Ala Gly Ala Leu Met Met Leu Val Gly Phe Leu Gly Cys Cys Gly
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Ala Val Gln Glu Ser Gln Cys Met Leu Gly Leu Phe Phe Gly Phe Leu
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Leu Val Ile Phe Ala Ile Glu Ile Ala Ala Ala Ile Trp Gly Tyr Ser
100 105 110

His Lys Asp Glu Val Ile Lys Glu Val Gln Glu Phe Tyr Lys Asp Thr
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Tyr Asn Lys Leu Lys Thr Lys Asp Glu Pro Gln Arg Glu Thr Leu Lys
130 135 140

Ala Ile His Tyr Ala Leu Asn Cys Cys Gly Leu Ala Gly Gly Val Glu
145 150 155 160

Gln Phe Ile Ser Asp Ile Cys Pro Lys Lys Asp Val Leu Glu Thr Phe
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Thr Val Lys Ser Cys Pro Asp Ala Ile Lys Glu Val Phe Asp Asn Lys
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Phe His Ile Ile Gly Ala Val Gly Ile Gly Ile Ala Val Val Met Ile
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Glu Pro Leu Ile Ile Ser Lys Val Glu Glu Gly Gly Lys Ala Asp Thr	
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Leu Thr Ser Gly Pro Gln His Arg Lys Ala Ala Trp Ser Gly Gly Val	
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Lys 145	Leu	Arg	Leu	Lys	His 150	Arg	Ser	Ser	Glu	Pro 155	Ala	Gly	Arg	Pro	His 160	
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Met	Gln	Ile	Ser	Gln	Gly	Met	Ile	Gly	Pro	Pro	Trp	His	Gln	Ser	Tyr	
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His	Ser	Ser	Ser	Ser	Thr	Ser	Asp	Leu	Ser	Asn	Tyr	Asp	His	Ala	Tyr	
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Ser	Thr	Gly	Ser	Ile	Asp	Gln	Leu	Ser	His	Phe	His	Asn	Lys	Arg	Asp	
				245					250					255		
tcg	gct	tac	agc	tct	ttc	tcc	acc	agt	tct	agc	atc	cta	gag	tat	cca	1773
Ser	Ala	Tyr	Ser	Ser	Phe	Ser	Thr	Ser	Ser	Ser	Ile	Leu	Glu	Tyr	Pro	
				260				265					270			
cac	cct	ggc	atc	tct	gcc	cgg	gag	cgt	tca	ggc	tcc	atg	gac	aat	act	1821
His	Pro	Gly	Ile	Ser	Ala	Arg	Glu	Arg	Ser	Gly	Ser	Met	Asp	Asn	Thr	
		275					280					285				
tct	gct	cga	ggg	ggc	ctc	ctc	gaa	ggg	atg	agg	cag	gca	gat	att	cgc	1869
Ser	Ala	Arg	Gly	Gly	Leu	Leu	Glu	Gly	Met	Arg	Gln	Ala	Asp	Ile	Arg	
	290					295					300					
tat	gtc	aag	aca	gtc	tat	gac	acc	cgg	agg	gga	gtc	tca	gca	gag	tat	1917
Tyr	Val	Lys	Thr	Val	Tyr	Asp	Thr	Arg	Arg	Gly	Val	Ser	Ala	Glu	Tyr	
305					310					315					320	
gag	gtg	aac	tct	tca	gcc	ctg	ctg	ctt	caa	ggg	agg	gag	gcc	cga	gcc	1965
Glu	Val	Asn	Ser	Ser	Ala	Leu	Leu	Leu	Gln	Gly	Arg	Glu	Ala	Arg	Ala	
				325					330					335		
tca	gca	aat	ggg	cag	ggc	tat	gat	aaa	tgg	tct	aat	att	cct	cgg	ggc	2013
Ser	Ala	Asn	Gly	Gln	Gly	Tyr	Asp	Lys	Trp	Ser	Asn	Ile	Pro	Arg	Gly	
			340					345					350			
aag	gga	gtg	cca	ccc	cca	tcc	tgg	agc	cag	cag	tgc	ccc	agt	tcc	ttg	2061
Lys	Gly	Val	Pro	Pro	Pro	Ser	Trp	Ser	Gln	Gln	Cys	Pro	Ser	Ser	Leu	
		355					360					365				
gag	act	gcc	acg	gac	aac	ctt	cct	cct	aag	gtg	ggg	gca	ccc	ctg	cct	2109
Glu	Thr	Ala	Thr	Asp	Asn	Leu	Pro	Pro	Lys	Val	Gly	Ala	Pro	Leu	Pro	
		370				375					380					
cca	gct	cgg	agt	gac	agt	tac	gca	gca	ttt	cgg	cac	cgt	gag	cgg	ccc	2157
Pro	Ala	Arg	Ser	Asp	Ser	Tyr	Ala	Ala	Phe	Arg	His	Arg	Glu	Arg	Pro	
385					390					395					400	
agc	tcc	tgg	tct	agc	ctt	gat	cag	aaa	cgg	ctc	tgc	cgg	cct	cag	gca	2205
Ser	Ser	Trp	Ser	Ser	Leu	Asp	Gln	Lys	Arg	Leu	Cys	Arg	Pro	Gln	Ala	
				405					410					415		
aac	tct	tta	ggc	tcc	ctg	aag	tct	cca	ttc	ata	gag	gag	cag	ctg	cat	2253

Asn Ser Leu Gly Ser Leu Lys Ser Pro Phe Ile Glu Glu Gln Leu His	
420 425 430	
act gtg ctg gag aag agt cca gag aac agc ccc cca gtg aag ccc aag	2301
Thr Val Leu Glu Lys Ser Pro Glu Asn Ser Pro Pro Val Lys Pro Lys	
435 440 445	
cat aac tat acc cag aag gcc caa cct ggc caa cct ctg ctg ccg acc	2349
His Asn Tyr Thr Gln Lys Ala Gln Pro Gly Gln Pro Leu Leu Pro Thr	
450 455 460	
agc atc tac gcg gta cct tcc ctg gag cca cac ttt gcc cag gtg cct	2397
Ser Ile Tyr Ala Val Pro Ser Leu Glu Pro His Phe Ala Gln Val Pro	
465 470 475 480	
cag cct tct gtg agt agc aac ggt atg ctc tac cct gca ctg gcc aag	2445
Gln Pro Ser Val Ser Ser Asn Gly Met Leu Tyr Pro Ala Leu Ala Lys	
485 490 495	
gag agt gga tac ata gcc cct cag gga gca tgc aac aag atg gct acc	2493
Glu Ser Gly Tyr Ile Ala Pro Gln Gly Ala Cys Asn Lys Met Ala Thr	
500 505 510	
att gat gag aat ggg aac cag aat gga tct ggc agg cct ggg ttt gcc	2541
Ile Asp Glu Asn Gly Asn Gln Asn Gly Ser Gly Arg Pro Gly Phe Ala	
515 520 525	
ttc tgc cag ccc tta gaa cat gac ttg ctg tcc cca gtg gag aag aaa	2589
Phe Cys Gln Pro Leu Glu His Asp Leu Leu Ser Pro Val Glu Lys Lys	
530 535 540	
cca gaa gct aca gcc aag tat gtc ccc tcc aaa gtc cat ttc tgt tca	2637
Pro Glu Ala Thr Ala Lys Tyr Val Pro Ser Lys Val His Phe Cys Ser	
545 550 555 560	
gtg cct gaa aat gag gag gat gcc tcc ctg aag aga cat ctc aca cct	2685
Val Pro Glu Asn Glu Glu Asp Ala Ser Leu Lys Arg His Leu Thr Pro	
565 570 575	
ccc caa ggc aac agc cca cat tcc aat gag aga aag agc acc cac agt	2733
Pro Gln Gly Asn Ser Pro His Ser Asn Glu Arg Lys Ser Thr His Ser	
580 585 590	
aac aaa cca tct tct cat ccc cac agc ctc aaa tgc cct cag gct cag	2781
Asn Lys Pro Ser Ser His Pro His Ser Leu Lys Cys Pro Gln Ala Gln	
595 600 605	
gcc tgg caa gcg ggt gaa gac aag aga tct tcc agg ctc tca gag ccc	2829
Ala Trp Gln Ala Gly Glu Asp Lys Arg Ser Ser Arg Leu Ser Glu Pro	
610 615 620	
tgg gag ggc gat ttc cag gaa gac cac aat gcc aac ctc tgg agg agg	2877
Trp Glu Gly Asp Phe Gln Glu Asp His Asn Ala Asn Leu Trp Arg Arg	
625 630 635 640	
ctg gag aga gaa ggc cta ggc cag agc ctg tca ggc aac ttt ggc aag	2925
Leu Glu Arg Glu Gly Leu Gly Gln Ser Leu Ser Gly Asn Phe Gly Lys	
645 650 655	
acc aag tca gcc ttc tca tct ctc cag aac att cct gag agt ctg aga	2973
Thr Lys Ser Ala Phe Ser Ser Leu Gln Asn Ile Pro Glu Ser Leu Arg	
660 665 670	
aga cac agc agc ctg gag cta gcc cgg gga acc cag gag ggt tac ccc	3021
Arg His Ser Ser Leu Glu Leu Gly Arg Gly Thr Gln Glu Gly Tyr Pro	
675 680 685	
ggg ggc agg ccc acc tgt gca gtc aac acc aag gca gaa gac cct ggg	3069

Gly	Gly	Arg	Pro	Thr	Cys	Ala	Val	Asn	Thr	Lys	Ala	Glu	Asp	Pro	Gly	
690						695					700					
agg	aaa	gcc	gct	cct	gac	ctc	ggg	agc	cat	ctg	gac	cgg	cag	gtt	tcc	3117
Arg	Lys	Ala	Ala	Pro	Asp	Leu	Gly	Ser	His	Leu	Asp	Arg	Gln	Val	Ser	
705					710					715					720	
tac	ccg	cgg	ccc	gag	ggg	agg	acc	ggt	gcc	tcg	gct	tct	ttc	aac	agc	3165
Tyr	Pro	Arg	Pro	Glu	Gly	Arg	Thr	Gly	Ala	Ser	Ala	Ser	Phe	Asn	Ser	
				725					730					735		
aca	gac	cca	agt	ccc	gaa	gag	ccg	cct	gcc	ccc	tcg	cac	ccg	cac	aca	3213
Thr	Asp	Pro	Ser	Pro	Glu	Glu	Pro	Pro	Ala	Pro	Ser	His	Pro	His	Thr	
			740					745					750			
tcc	agt	ctg	ggc	cgg	agg	ggg	ccc	ggc	cca	ggc	agc	gcc	tcg	gct	ctt	3261
Ser	Ser	Leu	Gly	Arg	Arg	Gly	Pro	Gly	Pro	Gly	Ser	Ala	Ser	Ala	Leu	
	755					760					765					
cag	ggc	ttt	cag	tac	ggg	aag	ccc	cac	tgc	tcg	gtg	ctg	gag	aag	gtc	3309
Gln	Gly	Phe	Gln	Tyr	Gly	Lys	Pro	His	Cys	Ser	Val	Leu	Glu	Lys	Val	
	770					775					780					
tcc	aaa	ttc	gag	cag	cga	gag	caa	ggg	agc	cag	aga	ccg	agt	gtg	ggc	3357
Ser	Lys	Phe	Glu	Gln	Arg	Glu	Gln	Gly	Ser	Gln	Arg	Pro	Ser	Val	Gly	
785					790					795					800	
ggc	tct	ggt	ttt	ggc	cat	aac	tat	agg	ccc	cac	agg	acc	gtc	tca	act	3405
Gly	Ser	Gly	Phe	Gly	His	Asn	Tyr	Arg	Pro	His	Arg	Thr	Val	Ser	Thr	
				805					810					815		
tcc	agt	act	tct	ggg	aat	gac	ttc	gag	gag	aca	aaa	gca	cac	att	cgt	3453
Ser	Ser	Thr	Ser	Gly	Asn	Asp	Phe	Glu	Glu	Thr	Lys	Ala	His	Ile	Arg	
			820					825						830		
ttc	tct	gag	tca	gct	gaa	ccc	cta	ggc	aac	ggg	gag	cag	cac	ttc	aaa	3501
Phe	Ser	Glu	Ser	Ala	Glu	Pro	Leu	Gly	Asn	Gly	Glu	Gln	His	Phe	Lys	
	835						840					845				
aac	ggg	gag	ctg	aag	ttg	gaa	gag	gct	tcc	cgg	cag	ccc	tgc	ggt	cag	3549
Asn	Gly	Glu	Leu	Lys	Leu	Glu	Glu	Ala	Ser	Arg	Gln	Pro	Cys	Gly	Gln	
	850					855					860					
cag	ctg	agc	gga	gga	gcg	tcg	gac	agc	ggc	cgt	ggc	ccc	cag	agg	ccg	3597
Gln	Leu	Ser	Gly	Gly	Ala	Ser	Asp	Ser	Gly	Arg	Gly	Pro	Gln	Arg	Pro	
865					870				875						880	
gac	gct	cgg	ctc	ctc	cgt	agc	cag	agc	acc	ttc	cag	ctc	tcc	agc	gag	3645
Asp	Ala	Arg	Leu	Leu	Arg	Ser	Gln	Ser	Thr	Phe	Gln	Leu	Ser	Ser	Glu	
				885					890					895		
cca	gag	agg	gag	ccc	gag	tgg	cgg	gac	agg	ccc	ggc	tcg	ccc	gaa	tcg	3693
Pro	Glu	Arg	Glu	Pro	Glu	Trp	Arg	Asp	Arg	Pro	Gly	Ser	Pro	Glu	Ser	
			900					905					910			
ccc	ctg	ctg	gat	gcc	ccc	ttc	agc	cgc	gcc	tac	cgg	aac	agc	atc	aag	3741
Pro	Leu	Leu	Asp	Ala	Pro	Phe	Ser	Arg	Ala	Tyr	Arg	Asn	Ser	Ile	Lys	
	915					920						925				
gac	gca	cag	tcc	cgt	gtc	ttg	ggg	gcc	acc	tcc	ttt	cga	cgt	cga	gac	3789
Asp	Ala	Gln	Ser	Arg	Val	Leu	Gly	Ala	Thr	Ser	Phe	Arg	Arg	Arg	Asp	
	930					935					940					
ctg	gag	ctg	ggg	gcg	ccc	gtg	gcg	tcg	agg	tcc	tgg	cgg	cca	cgg	cct	3837
Leu	Glu	Leu	Gly	Ala	Pro	Val	Ala	Ser	Arg	Ser	Trp	Arg	Pro	Arg	Pro	
945					950					955					960	
tcc	tcg	gcc	cac	gtg	ggg	ctg	cgg	agc	ccc	gag	gcg	tcg	gcc	tcc	gcc	3885

Ser	Ser	Ala	His	Val	Gly	Leu	Arg	Ser	Pro	Glu	Ala	Ser	Ala	Ser	Ala			
				965					970					975				
tcc	ccg	cac	acg	ccc	cgg	gag	cgg	cac	agc	gtg	acc	cct	gct	gag	ggc		3933	
Ser	Pro	His	Thr	Pro	Arg	Glu	Arg	His	Ser	Val	Thr	Pro	Ala	Glu	Gly			
				980					985					990				
gac	ctg	gcc	agg	ccc	gtg	ccc	cct	gcc	gcc	cgg	aga	ggt	gct	cgc	cgg		3981	
Asp	Leu	Ala	Arg	Pro	Val	Pro	Pro	Ala	Ala	Arg	Arg	Gly	Ala	Arg	Arg			
				995					1000					1005				
cgc	ctg	act	ccc	gag	cag	aag	aag	cgc	tcc	tac	tcg	gag	ccc	gag			4026	
Arg	Leu	Thr	Pro	Glu	Gln	Lys	Lys	Arg	Ser	Tyr	Ser	Glu	Pro	Glu				
				1010					1015					1020				
aag	atg	aac	gag	gtg	ggg	atc	gtg	gag	gag	gcc	gaa	ccg	gca	ccc			4071	
Lys	Met	Asn	Glu	Val	Gly	Ile	Val	Glu	Glu	Ala	Glu	Pro	Ala	Pro				
				1025					1030					1035				
ctg	ggc	ccg	cag	aga	aat	ggg	atg	cgT	ttc	ccg	gag	agc	agc	gtg			4116	
Leu	Gly	Pro	Gln	Arg	Asn	Gly	Met	Arg	Phe	Pro	Glu	Ser	Ser	Val				
				1040					1045					1050				
gcc	gac	cgg	cgC	cgT	ctc	ttc	gag	cgC	gat	ggc	aag	gcc	tgc	tcc			4161	
Ala	Asp	Arg	Arg	Arg	Leu	Phe	Glu	Arg	Asp	Gly	Lys	Ala	Cys	Ser				
				1055					1060					1065				
acg	ctc	agc	ctg	tcg	ggg	ccc	gag	ctg	aag	cag	ttc	cag	cag	agc			4206	
Thr	Leu	Ser	Leu	Ser	Gly	Pro	Glu	Leu	Lys	Gln	Phe	Gln	Gln	Ser				
				1070					1075					1080				
gcc	ctg	gcg	gac	tac	atc	cag	cgC	aag	acc	ggc	aag	cgg	cct	acc			4251	
Ala	Leu	Ala	Asp	Tyr	Ile	Gln	Arg	Lys	Thr	Gly	Lys	Arg	Pro	Thr				
				1085					1090					1095				
tcc	gcc	gcc	ggc	tgc	agc	ctc	cag	gag	ccc	ggg	cca	ctg	cgT	gag			4296	
Ser	Ala	Ala	Gly	Cys	Ser	Leu	Gln	Glu	Pro	Gly	Pro	Leu	Arg	Glu				
				1100					1105					1110				
cgC	gcc	cag	agT	gcc	tac	ctc	cag	ccc	ggc	ccc	gcg	gcg	ctc	gaa			4341	
Arg	Ala	Gln	Ser	Ala	Tyr	Leu	Gln	Pro	Gly	Pro	Ala	Ala	Leu	Glu				
				1115					1120					1125				
ggc	tcc	ggc	ctc	gcc	tcg	gcc	tcc	agc	ttg	agc	tca	ctg	cgg	gag			4386	
Gly	Ser	Gly	Leu	Ala	Ser	Ala	Ser	Ser	Leu	Ser	Ser	Leu	Arg	Glu				
				1130					1135					1140				
ccc	agc	ctg	cag	ccc	cgC	agg	gag	gcc	acg	ctc	ctg	ccg	gcc	aca			4431	
Pro	Ser	Leu	Gln	Pro	Arg	Arg	Glu	Ala	Thr	Leu	Leu	Pro	Ala	Thr				
				1145					1150					1155				
gtt	gca	gaa	acc	cag	cag	gct	ccc	cga	gat	cgC	agc	agc	tcc	ttc			4476	
Val	Ala	Glu	Thr	Gln	Gln	Ala	Pro	Arg	Asp	Arg	Ser	Ser	Ser	Phe				
				1160					1165					1170				
gcc	ggt	ggc	cgC	cgC	ctc	ggg	gaa	cgg	cga	cgC	ggg	gac	ctg	ctt			4521	
Ala	Gly	Gly	Arg	Arg	Leu	Gly												

Met Ser Ala Glu Asp Leu Leu Glu Arg Ser Asp Val Leu Ala Gly 1220 1225 1230	
cct gtc cat gtg agg tcc agg tca tct ccc gcc acc gca gac aag Pro Val His Val Arg Ser Arg Ser Ser Pro Ala Thr Ala Asp Lys 1235 1240 1245	4701
cgc cag gat gtg ctt ttg ggg caa gac agt ggc ttt ggt ctt gtg Arg Gln Asp Val Leu Leu Gly Gln Asp Ser Gly Phe Gly Leu Val 1250 1255 1260	4746
aag gat cca tgt tat ttg gct ggt cct gga tct agg tca ctc agt Lys Asp Pro Cys Tyr Leu Ala Gly Pro Gly Ser Arg Ser Leu Ser 1265 1270 1275	4791
tgt tca gaa aga ggc caa gaa gag atg ctg ctg ctc ttc cac cat Cys Ser Glu Arg Gly Gln Glu Glu Met Leu Leu Leu Phe His His 1280 1285 1290	4836
ctc acc cct cgt tgg ggt ggt tca ggc tgc aaa gcc att ggt gat Leu Thr Pro Arg Trp Gly Gly Ser Gly Cys Lys Ala Ile Gly Asp 1295 1300 1305	4881
tcc tcc gtt cct agt gaa tgt cct gga acc ctg gac cat cag agg Ser Ser Val Pro Ser Glu Cys Pro Gly Thr Leu Asp His Gln Arg 1310 1315 1320	4926
caa gcc agt agg aca ccc tgc ccc agg cca cca ctg gca gga acg Gln Ala Ser Arg Thr Pro Cys Pro Arg Pro Pro Leu Ala Gly Thr 1325 1330 1335	4971
caa ggg ctg gtc aca gac acc agg gct gca ccc ctg acc cca att Gln Gly Leu Val Thr Asp Thr Arg Ala Ala Pro Leu Thr Pro Ile 1340 1345 1350	5016
ggc acc cct ctg cct tca gcc att ccc tct ggc tac tgc tca cag Gly Thr Pro Leu Pro Ser Ala Ile Pro Ser Gly Tyr Cys Ser Gln 1355 1360 1365	5061
gac ggt cag aca ggg cga cag cct ctc ccg ccc tac acc cct gcc Asp Gly Gln Thr Gly Arg Gln Pro Leu Pro Pro Tyr Thr Pro Ala 1370 1375 1380	5106
atg atg cac aga agc aat ggt cac acc ctg acc cag cct ccc ggt Met Met His Arg Ser Asn Gly His Thr Leu Thr Gln Pro Pro Gly 1385 1390 1395	5151
cca aga ggc tgt gag ggc gat ggc cca gag cat ggg gta gaa gag Pro Arg Gly Cys Glu Gly Asp Gly Pro Glu His Gly Val Glu Glu 1400 1405 1410	5196
gga acg agg aag agg gtc tcg ctg cct cag tgg cca cct cct tct Gly Thr Arg Lys Arg Val Ser Leu Pro Gln Trp Pro Pro Pro Ser 1415 1420 1425	5241
cga gca aag tgg gcc cac gca gcc aga gag gac agc ctt cct gag Arg Ala Lys Trp Ala His Ala Ala Arg Glu Asp Ser Leu Pro Glu 1430 1435 1440	5286
gaa tcc tca gcc cct gat ttt gca aac ctg aag cac tat caa aaa Glu Ser Ser Ala Pro Asp Phe Ala Asn Leu Lys His Tyr Gln Lys 1445 1450 1455	5331
cag cag agt ctt cca agt tta tgc agc act tct gac cca gac aca Gln Gln Ser Leu Pro Ser Leu Cys Ser Thr Ser Asp Pro Asp Thr 1460 1465 1470	5376
cct ctt ggg gcc ccg agc act cca ggg agg atc tcc ctc cga ata	5421

Pro Leu Gly Ala Pro Ser Thr	Pro Gly Arg Ile Ser	Leu Arg Ile	
1475	1480	1485	
tct gag tct gtc ctg cgg gac	tcc ccg cca cct cat	gag gat tat	5466
Ser Glu Ser Val Leu Arg Asp	Ser Pro Pro Pro His	Glu Asp Tyr	
1490	1495	1500	
gaa gac gaa gtg ttt gtg agg	gat ccg cac ccc aag	gcc acg tcc	5511
Glu Asp Glu Val Phe Val Arg	Asp Pro His Pro Lys	Ala Thr Ser	
1505	1510	1515	
agc ccc aca ttt gaa cct ctt	ccc cca ccc cca cct	cct cca ccg	5556
Ser Pro Thr Phe Glu Pro Leu	Pro Pro Pro Pro Pro	Pro Pro Pro	
1520	1525	1530	
agt cag gaa acc ccg gtg tat	agc atg gat gac ttc	cct cca cct	5601
Ser Gln Glu Thr Pro Val Tyr	Ser Met Asp Asp Phe	Pro Pro Pro	
1535	1540	1545	
cct ccc cac act gta tgt gag	gcg cag ctg gac agt	gag gat ccc	5646
Pro Pro His Thr Val Cys Glu	Ala Gln Leu Asp Ser	Glu Asp Pro	
1550	1555	1560	
gag ggg cca cgc ccc agc ttc	aac aaa ctt tct aaa	gtg aca att	5691
Glu Gly Pro Arg Pro Ser Phe	Asn Lys Leu Ser Lys	Val Thr Ile	
1565	1570	1575	
gca agg gaa agg cac atg cct	ggt gca gcc cat gtg	gta ggt agt	5736
Ala Arg Glu Arg His Met Pro	Gly Ala Ala His Val	Val Gly Ser	
1580	1585	1590	
cag aca ctg gct tcc aga ctc	caa act tct atc aag	ggt tca gag	5781
Gln Thr Leu Ala Ser Arg Leu	Gln Thr Ser Ile Lys	Gly Ser Glu	
1595	1600	1605	
gct gag tcc aca cca ccc tcc	ttc atg agc gtt cac	gcc caa ctt	5826
Ala Glu Ser Thr Pro Pro Ser	Phe Met Ser Val His	Ala Gln Leu	
1610	1615	1620	
gct ggg tct ctt ggt ggg cag	cca gca ccc atc cag	act caa agc	5871
Ala Gly Ser Leu Gly Gly Gln	Pro Ala Pro Ile Gln	Thr Gln Ser	
1625	1630	1635	
ctc agc cat gat cca gtc agt	gga act cag ggt tta	gaa aag aaa	5916
Leu Ser His Asp Pro Val Ser	Gly Thr Gln Gly Leu	Glu Lys Lys	
1640	1645	1650	
gtc agt cct gat cct cag aag	agt tca gaa gac atc	aga aca gag	5961
Val Ser Pro Asp Pro Gln Lys	Ser Ser Glu Asp Ile	Arg Thr Glu	
1655	1660	1665	
gct ttg gcc aag gaa att gtc	cac caa gac aaa tct	cta gca gac	6006
Ala Leu Ala Lys Glu Ile Val	His Gln Asp Lys Ser	Leu Ala Asp	
1670	1675	1680	
att ttg gat cca gac tcc agg	ctg aag aca aca atg	gac ctg atg	6051
Ile Leu Asp Pro Asp Ser Arg	Leu Lys Thr Thr Met	Asp Leu Met	
1685	1690	1695	
gaa ggt ttg ttt ccc cga gat	gtg aac ttg ctg aag	gaa aac agt	6096
Glu Gly Leu Phe Pro Arg Asp	Val Asn Leu Leu Lys	Glu Asn Ser	
1700	1705	1710	
gta aag agg aag gcc ata cag	aga act gtc agc tct	tca gga tgt	6141
Val Lys Arg Lys Ala Ile Gln	Arg Thr Val Ser Ser	Ser Gly Cys	
1715	1720	1725	
gaa ggc aag agg aat gaa gac	aag gaa gca gtg agc	atg ttg gtt	6186

Glu Gly	Lys Arg Asn Glu Asp	Lys Glu Ala Val Ser	Met Leu Val	
1730	1735	1740		
aac tgc	cct gcc tac tac agt	gtg tct gct ccc aag	gct gag cta	6231
Asn Cys	Pro Ala Tyr Tyr Ser	Val Ser Ala Pro Lys	Ala Glu Leu	
1745	1750	1755		
ctg aac	aaa atc aaa gag atg	cca gca gaa gtg aat	gag gaa gag	6276
Leu Asn	Lys Ile Lys Glu Met	Pro Ala Glu Val Asn	Glu Glu Glu	
1760	1765	1770		
gaa cag	gca gat gtc aat gaa	aag aag gct gag ctc	att gga agt	6321
Glu Gln	Ala Asp Val Asn Glu	Lys Lys Ala Glu Leu	Ile Gly Ser	
1775	1780	1785		
ctc acc	cac aag ctg gag acc	ctc cag gag gcg aag	ggg agc ctg	6366
Leu Thr	His Lys Leu Glu Thr	Leu Gln Glu Ala Lys	Gly Ser Leu	
1790	1795	1800		
ctc acg	gac atc aag ctc aac	aac gcc ctg gga gaa	gag gtg gag	6411
Leu Thr	Asp Ile Lys Leu Asn	Asn Ala Leu Gly Glu	Glu Val Glu	
1805	1810	1815		
gct ctg	atc agc gag ctc tgc	aag ccc aat gag ttt	gac aag tat	6456
Ala Leu	Ile Ser Glu Leu Cys	Lys Pro Asn Glu Phe	Asp Lys Tyr	
1820	1825	1830		
agg atg	ttc ata ggg gat ttg	gac aag gtg gtc aac	ctg ctg ctc	6501
Arg Met	Phe Ile Gly Asp Leu	Asp Lys Val Val Asn	Leu Leu Leu	
1835	1840	1845		
tcc ctc	tcg ggg cgt cta gcc	cgt gtt gag aat gtc	ctt agc ggc	6546
Ser Leu	Ser Gly Arg Leu Ala	Arg Val Glu Asn Val	Leu Ser Gly	
1850	1855	1860		
ctt ggt	gaa gat gcc agt aat	gaa gaa agg agc tct	ctt tac gag	6591
Leu Gly	Glu Asp Ala Ser Asn	Glu Glu Arg Ser Ser	Leu Tyr Glu	
1865	1870	1875		
aaa agg	aag atc ctg gct ggt	cag cat gag gat gcc	cgg gag ctg	6636
Lys Arg	Lys Ile Leu Ala Gly	Gln His Glu Asp Ala	Arg Glu Leu	
1880	1885	1890		
aag gag	aac ctg gat cgc agg	gag cga gta gtg ctg	ggc atc ttg	6681
Lys Glu	Asn Leu Asp Arg Arg	Glu Arg Val Val Leu	Gly Ile Leu	
1895	1900	1905		
gcc aat	tac ctt tca gag gag	cag ctc cag gac tac	cag cac ttc	6726
Ala Asn	Tyr Leu Ser Glu Glu	Gln Leu Gln Asp Tyr	Gln His Phe	
1910	1915	1920		
gtg aaa	atg aag tcc acg ctc	ctc att gag caa cgg	aag ctg gat	6771
Val Lys	Met Lys Ser Thr Leu	Leu Ile Glu Gln Arg	Lys Leu Asp	
1925	1930	1935		
gac aag	atc aag ctg ggc cag	gag cag gtc aag tgt	ctg ctg gag	6816
Asp Lys	Ile Lys Leu Gly Gln	Glu Gln Val Lys Cys	Leu Leu Glu	
1940	1945	1950		
agc ctg	ccc tca gat ttc att	ccc aag gct ggg gcc	ctg gct ctg	6861
Ser Leu	Pro Ser Asp Phe Ile	Pro Lys Ala Gly Ala	Leu Ala Leu	
1955	1960	1965		
ccc cca	aac ctc acg agt gag	ccc att cct gct ggg	ggc tgt act	6906
Pro Pro	Asn Leu Thr Ser Glu	Pro Ile Pro Ala Gly	Gly Cys Thr	
1970	1975	1980		
ttc agt	ggt att ttc cca aca	tta acc tct cca ctt	taacctcttc	6952

Phe Ser Gly Ile Phe Pro Thr Leu Thr Ser Pro Leu
 1985 1990 1995

taaaataccc aaccaaaga tcaactgttc tctcaacact atttaactctg aaaaatgttt 7012

cagtacaaac cactgtttga actatctggg ttattggtgt ttgttcctga tgaaaggaaa 7072

aaaattctct ccaggaggaa gcctttttcc ttcttgccct tctgattga tcttctgaga 7132

gctcgaatgc tgctggacac gtaccccttt ctattattac ttgtagtag aaagaaagt 7192

aatgaaactg agaactgatt ggagggtgt tgatcattta gttttaaca ggctgaggca 7252

acatggatca gtgtgtgtcc ccctcaggaa tgtatccaca gtggccttcc ttgctggtgg 7312

gcagtgtatc ctgatggcag ggtacaagta ccattaatga aggtctgca acataaagcc 7372

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aatggaaaa gatcactatg ttgtgtgtgc taaccactta ttgattctg tttgtggtg 7492

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<400> 38

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Gly Gly Ala Pro Trp Gly Phe Thr Leu Lys Gly Gly Leu Glu His Gly
 35 40 45

Glu Pro Leu Ile Ile Ser Lys Val Glu Glu Gly Gly Lys Ala Asp Thr
 50 55 60

Leu Ser Ser Lys Leu Gln Ala Gly Asp Glu Val Val His Ile Asn Glu
 65 70 75 80

Val Thr Leu Ser Ser Ser Arg Lys Glu Ala Val Ser Leu Val Lys Gly
 85 90 95

Ser Tyr Lys Thr Leu Arg Leu Val Val Arg Arg Asp Val Cys Thr Asp
 100 105 110

Pro Gly His Ala Asp Thr Gly Ala Ser Asn Phe Val Ser Pro Glu His
 115 120 125

Leu Thr Ser Gly Pro Gln His Arg Lys Ala Ala Trp Ser Gly Gly Val
 130 135 140

Lys Leu Arg Leu Lys His Arg Ser Ser Glu Pro Ala Gly Arg Pro His
 145 150 155 160

Ser Trp His Thr Thr Lys Ser Gly Glu Lys Gln Pro Asp Ala Ser Met
 165 170 175

Met Gln Ile Ser Gln Gly Met Ile Gly Pro Pro Trp His Gln Ser Tyr
 180 185 190

His Ser Ser Ser Ser Thr Ser Asp Leu Ser Asn Tyr Asp His Ala Tyr
 195 200 205

Leu Arg Arg Ser Pro Asp Gln Cys Ser Ser Gln Gly Ser Met Glu Ser
 210 215 220

Leu Glu Pro Ser Gly Ala Tyr Pro Pro Cys His Leu Ser Pro Ala Lys
 225 230 235 240

Ser Thr Gly Ser Ile Asp Gln Leu Ser His Phe His Asn Lys Arg Asp
 245 250 255

Ser Ala Tyr Ser Ser Phe Ser Thr Ser Ser Ser Ile Leu Glu Tyr Pro
 260 265 270

His Pro Gly Ile Ser Ala Arg Glu Arg Ser Gly Ser Met Asp Asn Thr
 275 280 285

Ser Ala Arg Gly Gly Leu Leu Glu Gly Met Arg Gln Ala Asp Ile Arg
 290 295 300

Tyr Val Lys Thr Val Tyr Asp Thr Arg Arg Gly Val Ser Ala Glu Tyr
 305 310 315 320

Glu Val Asn Ser Ser Ala Leu Leu Leu Gln Gly Arg Glu Ala Arg Ala
 325 330 335

Ser Ala Asn Gly Gln Gly Tyr Asp Lys Trp Ser Asn Ile Pro Arg Gly
 340 345 350

Lys Gly Val Pro Pro Pro Ser Trp Ser Gln Gln Cys Pro Ser Ser Leu
 355 360 365

Glu Thr Ala Thr Asp Asn Leu Pro Pro Lys Val Gly Ala Pro Leu Pro
 370 375 380

Pro Ala Arg Ser Asp Ser Tyr Ala Ala Phe Arg His Arg Glu Arg Pro
 385 390 395 400

Ser Ser Trp Ser Ser Leu Asp Gln Lys Arg Leu Cys Arg Pro Gln Ala
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Asn Ser Leu Gly Ser Leu Lys Ser Pro Phe Ile Glu Glu Gln Leu His
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Thr Val Leu Glu Lys Ser Pro Glu Asn Ser Pro Pro Val Lys Pro Lys
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His Asn Tyr Thr Gln Lys Ala Gln Pro Gly Gln Pro Leu Leu Pro Thr
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Ser Ile Tyr Ala Val Pro Ser Leu Glu Pro His Phe Ala Gln Val Pro
 465 470 475 480

Gln Pro Ser Val Ser Ser Asn Gly Met Leu Tyr Pro Ala Leu Ala Lys
 485 490 495

Glu Ser Gly Tyr Ile Ala Pro Gln Gly Ala Cys Asn Lys Met Ala Thr
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Ile Asp Glu Asn Gly Asn Gln Asn Gly Ser Gly Arg Pro Gly Phe Ala
 515 520 525

Phe Cys Gln Pro Leu Glu His Asp Leu Leu Ser Pro Val Glu Lys Lys
 530 535 540

Pro Glu Ala Thr Ala Lys Tyr Val Pro Ser Lys Val His Phe Cys Ser
 545 550 555 560

Val Pro Glu Asn Glu Glu Asp Ala Ser Leu Lys Arg His Leu Thr Pro
 565 570 575

Pro Gln Gly Asn Ser Pro His Ser Asn Glu Arg Lys Ser Thr His Ser
 580 585 590

Asn Lys Pro Ser Ser His Pro His Ser Leu Lys Cys Pro Gln Ala Gln
 595 600 605

Ala Trp Gln Ala Gly Glu Asp Lys Arg Ser Ser Arg Leu Ser Glu Pro
 610 615 620

Trp Glu Gly Asp Phe Gln Glu Asp His Asn Ala Asn Leu Trp Arg Arg
 625 630 635 640

Leu Glu Arg Glu Gly Leu Gly Gln Ser Leu Ser Gly Asn Phe Gly Lys
 645 650 655

Thr Lys Ser Ala Phe Ser Ser Leu Gln Asn Ile Pro Glu Ser Leu Arg
 660 665 670

Arg His Ser Ser Leu Glu Leu Gly Arg Gly Thr Gln Glu Gly Tyr Pro
 675 680 685

Gly Gly Arg Pro Thr Cys Ala Val Asn Thr Lys Ala Glu Asp Pro Gly
 690 695 700

Arg Lys Ala Ala Pro Asp Leu Gly Ser His Leu Asp Arg Gln Val Ser
 705 710 715 720

Tyr Pro Arg Pro Glu Gly Arg Thr Gly Ala Ser Ala Ser Phe Asn Ser
 725 730 735

Thr Asp Pro Ser Pro Glu Glu Pro Pro Ala Pro Ser His Pro His Thr
 740 745 750

Ser Ser Leu Gly Arg Arg Gly Pro Gly Pro Gly Ser Ala Ser Ala Leu
 755 760 765

Gln Gly Phe Gln Tyr Gly Lys Pro His Cys Ser Val Leu Glu Lys Val
 770 775 780

Ser Lys Phe Glu Gln Arg Glu Gln Gly Ser Gln Arg Pro Ser Val Gly
 785 790 795 800

Gly Ser Gly Phe Gly His Asn Tyr Arg Pro His Arg Thr Val Ser Thr
 805 810 815

Ser Ser Thr Ser Gly Asn Asp Phe Glu Glu Thr Lys Ala His Ile Arg
 820 825 830

Phe Ser Glu Ser Ala Glu Pro Leu Gly Asn Gly Glu Gln His Phe Lys
 835 840 845

Asn Gly Glu Leu Lys Leu Glu Glu Ala Ser Arg Gln Pro Cys Gly Gln
 850 855 860

Gln Leu Ser Gly Gly Ala Ser Asp Ser Gly Arg Gly Pro Gln Arg Pro
 865 870 875 880

Asp Ala Arg Leu Leu Arg Ser Gln Ser Thr Phe Gln Leu Ser Ser Glu
 885 890 895

Pro Glu Arg Glu Pro Glu Trp Arg Asp Arg Pro Gly Ser Pro Glu Ser
 900 905 910

Pro Leu Leu Asp Ala Pro Phe Ser Arg Ala Tyr Arg Asn Ser Ile Lys
 915 920 925

Asp Ala Gln Ser Arg Val Leu Gly Ala Thr Ser Phe Arg Arg Arg Asp
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Leu Glu Leu Gly Ala Pro Val Ala Ser Arg Ser Trp Arg Pro Arg Pro
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Ser Ser Ala His Val Gly Leu Arg Ser Pro Glu Ala Ser Ala Ser Ala
 965 970 975

Ser Pro His Thr Pro Arg Glu Arg His Ser Val Thr Pro Ala Glu Gly
 980 985 990

Asp Leu Ala Arg Pro Val Pro Pro Ala Ala Arg Arg Gly Ala Arg Arg
 995 1000 1005

Arg Leu Thr Pro Glu Gln Lys Lys Arg Ser Tyr Ser Glu Pro Glu
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Lys Met Asn Glu Val Gly Ile Val Glu Glu Ala Glu Pro Ala Pro
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Leu Gly Pro Gln Arg Asn Gly Met Arg Phe Pro Glu Ser Ser Val
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Thr Leu Ser Leu Ser Gly Pro Glu Leu Lys Gln Phe Gln Gln Ser
 1070 1075 1080

Ala Leu Ala Asp Tyr Ile Gln Arg Lys Thr Gly Lys Arg Pro Thr
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Ser Ala Ala Gly Cys Ser Leu Gln Glu Pro Gly Pro Leu Arg Glu
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Arg Ala Gln Ser Ala Tyr Leu Gln Pro Gly Pro Ala Ala Leu Glu
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Gly Ser Gly Leu Ala Ser Ala Ser Ser Leu Ser Ser Leu Arg Glu
 1130 1135 1140

Pro Ser Leu Gln Pro Arg Arg Glu Ala Thr Leu Leu Pro Ala Thr
 1145 1150 1155

Val Ala Glu Thr Gln Gln Ala Pro Arg Asp Arg Ser Ser Ser Phe
 1160 1165 1170

Ala Gly Gly Arg Arg Leu Gly Glu Arg Arg Arg Gly Asp Leu Leu
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Ser Gly Ala Asn Gly Gly Thr Arg Gly Thr Gln Arg Gly Asp Glu
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Thr Pro Arg Glu Pro Ser Ser Trp Gly Ala Arg Ala Gly Lys Ser
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 Met Ser Ala Glu Asp Leu Leu Glu Arg Ser Asp Val Leu Ala Gly
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 Pro Val His Val Arg Ser Arg Ser Ser Pro Ala Thr Ala Asp Lys
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 Arg Gln Asp Val Leu Leu Gly Gln Asp Ser Gly Phe Gly Leu Val
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 Lys Asp Pro Cys Tyr Leu Ala Gly Pro Gly Ser Arg Ser Leu Ser
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 Cys Ser Glu Arg Gly Gln Glu Glu Met Leu Leu Leu Phe His His
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 Leu Thr Pro Arg Trp Gly Gly Ser Gly Cys Lys Ala Ile Gly Asp
 1295 1300 1305
 Ser Ser Val Pro Ser Glu Cys Pro Gly Thr Leu Asp His Gln Arg
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 Gln Ala Ser Arg Thr Pro Cys Pro Arg Pro Pro Leu Ala Gly Thr
 1325 1330 1335
 Gln Gly Leu Val Thr Asp Thr Arg Ala Ala Pro Leu Thr Pro Ile
 1340 1345 1350
 Gly Thr Pro Leu Pro Ser Ala Ile Pro Ser Gly Tyr Cys Ser Gln
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 Pro Arg Gly Cys Glu Gly Asp Gly Pro Glu His Gly Val Glu Glu
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 Glu Ser Ser Ala Pro Asp Phe Ala Asn Leu Lys His Tyr Gln Lys
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Gln Gln Ser Leu Pro Ser Leu Cys Ser Thr Ser Asp Pro Asp Thr
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Pro Leu Gly Ala Pro Ser Thr Pro Gly Arg Ile Ser Leu Arg Ile
1475 1480 1485

Ser Glu Ser Val Leu Arg Asp Ser Pro Pro Pro His Glu Asp Tyr
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Glu Asp Glu Val Phe Val Arg Asp Pro His Pro Lys Ala Thr Ser
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Ser Gln Glu Thr Pro Val Tyr Ser Met Asp Asp Phe Pro Pro Pro
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Pro Pro His Thr Val Cys Glu Ala Gln Leu Asp Ser Glu Asp Pro
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Glu Gly Pro Arg Pro Ser Phe Asn Lys Leu Ser Lys Val Thr Ile
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Gln Thr Leu Ala Ser Arg Leu Gln Thr Ser Ile Lys Gly Ser Glu
1595 1600 1605

Ala Glu Ser Thr Pro Pro Ser Phe Met Ser Val His Ala Gln Leu
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Ala Gly Ser Leu Gly Gly Gln Pro Ala Pro Ile Gln Thr Gln Ser
1625 1630 1635

Leu Ser His Asp Pro Val Ser Gly Thr Gln Gly Leu Glu Lys Lys
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Val Ser Pro Asp Pro Gln Lys Ser Ser Glu Asp Ile Arg Thr Glu
1655 1660 1665

Ala Leu Ala Lys Glu Ile Val His Gln Asp Lys Ser Leu Ala Asp
1670 1675 1680

Ile Leu Asp Pro Asp Ser Arg Leu Lys Thr Thr Met Asp Leu Met
1685 1690 1695

Glu Gly Leu Phe Pro Arg Asp Val Asn Leu Leu Lys Glu Asn Ser
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Val Lys Arg Lys Ala Ile Gln Arg Thr Val Ser Ser Ser Gly Cys
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Glu Gly Lys Arg Asn Glu Asp Lys Glu Ala Val Ser Met Leu Val
 1730 1735 1740

Asn Cys Pro Ala Tyr Tyr Ser Val Ser Ala Pro Lys Ala Glu Leu
 1745 1750 1755

Leu Asn Lys Ile Lys Glu Met Pro Ala Glu Val Asn Glu Glu Glu
 1760 1765 1770

Glu Gln Ala Asp Val Asn Glu Lys Lys Ala Glu Leu Ile Gly Ser
 1775 1780 1785

Leu Thr His Lys Leu Glu Thr Leu Gln Glu Ala Lys Gly Ser Leu
 1790 1795 1800

Leu Thr Asp Ile Lys Leu Asn Asn Ala Leu Gly Glu Glu Val Glu
 1805 1810 1815

Ala Leu Ile Ser Glu Leu Cys Lys Pro Asn Glu Phe Asp Lys Tyr
 1820 1825 1830

Arg Met Phe Ile Gly Asp Leu Asp Lys Val Val Asn Leu Leu Leu
 1835 1840 1845

Ser Leu Ser Gly Arg Leu Ala Arg Val Glu Asn Val Leu Ser Gly
 1850 1855 1860

Leu Gly Glu Asp Ala Ser Asn Glu Glu Arg Ser Ser Leu Tyr Glu
 1865 1870 1875

Lys Arg Lys Ile Leu Ala Gly Gln His Glu Asp Ala Arg Glu Leu
 1880 1885 1890

Lys Glu Asn Leu Asp Arg Arg Glu Arg Val Val Leu Gly Ile Leu
 1895 1900 1905

Ala Asn Tyr Leu Ser Glu Glu Gln Leu Gln Asp Tyr Gln His Phe
 1910 1915 1920

Val Lys Met Lys Ser Thr Leu Leu Ile Glu Gln Arg Lys Leu Asp
 1925 1930 1935

Asp Lys Ile Lys Leu Gly Gln Glu Gln Val Lys Cys Leu Leu Glu
 1940 1945 1950

Ser Leu Pro Ser Asp Phe Ile Pro Lys Ala Gly Ala Leu Ala Leu
 1955 1960 1965

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35 40 45

Met Ser Leu Glu Gly Thr Glu Lys Ala Ser Trp Leu Gly Glu Gln Pro
50 55 60

Gln Phe Trp Ser Lys Thr Gln Val Leu Asp Trp Ile Ser Tyr Gln Val
65 70 75 80

Glu Lys Asn Lys Tyr Asp Ala Ser Ala Ile Asp Phe Ser Arg Cys Asp
85 90 95

Met Asp Gly Ala Thr Leu Cys Asn Cys Ala Leu Glu Glu Leu Arg Leu
100 105 110

Val Phe Gly Pro Leu Gly Asp Gln Leu His Ala Gln Leu Arg Asp Leu
115 120 125

Thr Ser Ser Ser Ser Asp Glu Leu Ser Trp Ile Ile Glu Leu Leu Glu
130 135 140

Lys Asp Gly Met Ala Phe Gln Glu Ala Leu Asp Pro Gly Pro Phe Asp
145 150 155 160

Gln Gly Ser Pro Phe Ala Gln Glu Leu Leu Asp Asp Gly Gln Gln Ala
165 170 175

Ser Pro Tyr His Pro Gly Ser Cys Gly Ala Gly Ala Pro Ser Pro Gly
180 185 190

Ser Ser Asp Val Ser Thr Ala Gly Thr Gly Ala Ser Arg Ser Ser His
195 200 205

Ser Ser Asp Ser Gly Gly Ser Asp Val Asp Leu Asp Pro Thr Asp Gly
210 215 220

Lys Leu Phe Pro Ser Asp Gly Phe Arg Asp Cys Lys Lys Gly Asp Pro
225 230 235 240

Lys His Gly Lys Arg Lys Arg Gly Arg Pro Arg Lys Leu Ser Lys Glu
245 250 255

Tyr Trp Asp Cys Leu Glu Gly Lys Lys Ser Lys His Ala Pro Arg Gly
260 265 270

Thr His Leu Trp Glu Phe Ile Arg Asp Ile Leu Ile His Pro Glu Leu
275 280 285

Asn Glu Gly Leu Met Lys Trp Glu Asn Arg His Glu Gly Val Phe Lys
290 295 300

Phe Leu Arg Ser Glu Ala Val Ala Gln Leu Trp Gly Gln Lys Lys Lys
305 310 315 320

Asn Ser Asn Met Thr Tyr Glu Lys Leu Ser Arg Ala Met Arg Tyr Tyr
325 330 335

Tyr Lys Arg Glu Ile Leu Glu Arg Val Asp Gly Arg Arg Leu Val Tyr

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 Glu Asn Gly Gln Arg Lys Tyr Gly Gly Pro Pro Pro Gly Trp Glu Gly
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 Pro His Pro Gln Arg Gly Cys Glu Val Phe Val Gly Lys Ile Pro Arg
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gag ctg gag ggc tgc tgc ctg gag gtc acg ctg gcc aag ccc gtg gac Glu Leu Glu Gly Ser Cys Leu Glu Val Thr Leu Ala Lys Pro Val Asp 305 310 315 320	1199
aag gag cag tac tgc cgc tac cag aag gca gcc agg ggc ggc ggc gcg Lys Glu Gln Tyr Ser Arg Tyr Gln Lys Ala Ala Arg Gly Gly Gly Ala 325 330 335	1247
gct gag gca gcg cag cag ccc agc tac gtg tac tcc tgc gac ccc tac Ala Glu Ala Ala Gln Gln Pro Ser Tyr Val Tyr Ser Cys Asp Pro Tyr 340 345 350	1295
aca ctg gcc tac tac ggc tac ccc tac aac gcg ctc att ggc ccc aac Thr Leu Ala Tyr Tyr Gly Tyr Pro Tyr Asn Ala Leu Ile Gly Pro Asn 355 360 365	1343
agg gac tac ttt gtg aaa gta gcc atc cct gcc att ggc gct cag tat Arg Asp Tyr Phe Val Lys Val Ala Ile Pro Ala Ile Gly Ala Gln Tyr 370 375 380	1391

tcc atg ttt cca gca gct cca gcc cct aaa atg att gaa gat ggc aaa Ser Met Phe Pro Ala Ala Pro Ala Pro Lys Met Ile Glu Asp Gly Lys 385 390 395 400	1439
atc cac aca gtg gag cac atg atc agc ccc att gct gtg cag cca gac Ile His Thr Val Glu His Met Ile Ser Pro Ile Ala Val Gln Pro Asp 405 410 415	1487
cca gcc agt gct gct gcc gcc gca gcc gcg gcc gca gcc gcc gca gcc Pro Ala Ser Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala 420 425 430	1535
gct gtc att ccc act gtg tcg acg cca cca cct ttc cag ggc cgc cca Ala Val Ile Pro Thr Val Ser Thr Pro Pro Pro Phe Gln Gly Arg Pro 435 440 445	1583
ata act cca gta tac acg gtg gct cca aac gtt cag aga att cct act Ile Thr Pro Val Tyr Thr Val Ala Pro Asn Val Gln Arg Ile Pro Thr 450 455 460	1631
gcc ggg atc tac ggg gcc agt tac gtg cca ttt gct gct cca gct aca Ala Gly Ile Tyr Gly Ala Ser Tyr Val Pro Phe Ala Ala Pro Ala Thr 465 470 475 480	1679
gcc acg atc gcc aca cta cag aag aac gcg gca gcc gcg gcc gcc gtg Ala Thr Ile Ala Thr Leu Gln Lys Asn Ala Ala Ala Ala Ala Val 485 490 495	1727
tat gga gga tac gca ggc tac ata cct cag gcc ttc cct gct gct gcc Tyr Gly Gly Tyr Ala Gly Tyr Ile Pro Gln Ala Phe Pro Ala Ala Ala 500 505 510	1775
att cag gtc ccc atc ccc gac gtc tac cag aca tac tgaggtggt Ile Gln Val Pro Ile Pro Asp Val Tyr Gln Thr Tyr 515 520	1821
gaccagcagc aagacagacc acacaaacac cactgaagga acgcttgact atttatgaag	1881
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ctgaattatt ttatatacat gaagttttca ctagtgtttt aagactattt tcaacttagc	2001
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tatatatttca gtatgaaggt tattttctta acttctgcac tccagagatt tctattttgt	2181
agtaccttca ataatatatc aactatatat taaaaaagca cacttgagga gctagggaac	2241
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taaagcatta ttttaaagggt tatactggaa agtgcaattt taaaatgagt aaacctctg	2361
tatttctgct ggcattaagg gttgatgggt ttaccatgta tcatcatggc ggtactattt	2421
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gagctggtgg cttttatact tcttctctggg tttttgttgg ggtttgttgt ttcgttgtt	2721
tttgtttttt ttttgtttgg ttggggaagt attgtcttct acgtgtgcta ttttcagtag	2781

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 gcccaatgta aaactttaat gccatttcta atgcttttat tcatttttga agtatgagtt 2901
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 aagttatgct tctagttgcc ttaccatggt tcttgcaaaa ctgtccatgg tcctcaaggg 3021
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 cttttgtttt gttttaaat aagagattcc caaatgcctt tttccccctc atcttgaaat 3621
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<211> 524

<212> PRT

<213> NM_019027 FLJ20273

<400> 42

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Ala Ala Leu Leu Ala Leu Met Glu Arg Thr Gly Tyr Ser Met Val Gln
 35 40 45

Glu Asn Gly Gln Arg Lys Tyr Gly Gly Pro Pro Pro Gly Trp Glu Gly

50 55 60
 Pro His Pro Gln Arg Gly Cys Glu Val Phe Val Gly Lys Ile Pro Arg
 65 70 75 80
 Asp Val Tyr Glu Asp Glu Leu Val Pro Val Phe Glu Ala Val Gly Arg
 85 90 95
 Thr Tyr Glu Leu Arg Leu Met Met Asp Phe Asp Gly Lys Asn Arg Gly
 100 105 110
 Tyr Ala Phe Val Met Tyr Cys His Lys His Glu Ala Lys Arg Ala Val
 115 120 125
 Arg Glu Leu Asn Asn Tyr Glu Ile Arg Pro Gly Arg Leu Leu Gly Val
 130 135 140
 Cys Cys Ser Val Asp Asn Cys Arg Leu Phe Ile Gly Gly Ile Pro Lys
 145 150 155 160
 Met Lys Lys Arg Glu Glu Ile Leu Glu Glu Ile Ala Lys Val Thr Glu
 165 170 175
 Gly Val Leu Asp Val Ile Val Tyr Ala Ser Ala Ala Asp Lys Met Lys
 180 185 190
 Asn Arg Gly Phe Ala Phe Val Glu Tyr Glu Ser His Arg Ala Ala Ala
 195 200 205
 Met Ala Arg Arg Lys Leu Met Pro Gly Arg Ile Gln Leu Trp Gly His
 210 215 220
 Gln Ile Ala Val Asp Trp Ala Glu Pro Glu Ile Asp Val Asp Glu Asp
 225 230 235 240
 Val Met Glu Thr Val Lys Ile Leu Tyr Val Arg Asn Leu Met Ile Glu
 245 250 255
 Thr Thr Glu Asp Thr Ile Lys Lys Ser Phe Gly Gln Phe Asn Pro Gly
 260 265 270
 Cys Val Glu Arg Val Lys Lys Ile Arg Asp Tyr Ala Phe Val His Phe
 275 280 285
 Thr Ser Arg Glu Asp Ala Val His Ala Met Asn Asn Leu Asn Gly Thr
 290 295 300
 Glu Leu Glu Gly Ser Cys Leu Glu Val Thr Leu Ala Lys Pro Val Asp
 305 310 315 320
 Lys Glu Gln Tyr Ser Arg Tyr Gln Lys Ala Ala Arg Gly Gly Gly Ala

325 330 335
 Ala Glu Ala Ala Gln Gln Pro Ser Tyr Val Tyr Ser Cys Asp Pro Tyr
 340 345 350
 Thr Leu Ala Tyr Tyr Gly Tyr Pro Tyr Asn Ala Leu Ile Gly Pro Asn
 355 360 365
 Arg Asp Tyr Phe Val Lys Val Ala Ile Pro Ala Ile Gly Ala Gln Tyr
 370 375 380
 Ser Met Phe Pro Ala Ala Pro Ala Pro Lys Met Ile Glu Asp Gly Lys
 385 390 395 400
 Ile His Thr Val Glu His Met Ile Ser Pro Ile Ala Val Gln Pro Asp
 405 410 415
 Pro Ala Ser Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala Ala
 420 425 430
 Ala Val Ile Pro Thr Val Ser Thr Pro Pro Pro Phe Gln Gly Arg Pro
 435 440 445
 Ile Thr Pro Val Tyr Thr Val Ala Pro Asn Val Gln Arg Ile Pro Thr
 450 455 460
 Ala Gly Ile Tyr Gly Ala Ser Tyr Val Pro Phe Ala Ala Pro Ala Thr
 465 470 475 480
 Ala Thr Ile Ala Thr Leu Gln Lys Asn Ala Ala Ala Ala Ala Ala Val
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<210> 43

<211> 1451

<212> DNA

<213> NM_013952 PAX8

<220>

<221> CDS

<222> (161)..(1354)

<223>

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 230 235 240 245
 cca gag gcc tat gcc tcc ccc agc cac acc aaa ggc gag cag gcc ctc 943
 Pro Glu Ala Tyr Ala Ser Pro Ser His Thr Lys Gly Glu Gln Gly Leu
 250 255 260
 tac ccg ctg ccc ttg ctc aac agc acc ctg gac gac ggg aag gcc acc 991
 Tyr Pro Leu Pro Leu Leu Asn Ser Thr Leu Asp Asp Gly Lys Ala Thr
 265 270 275
 ctg acc cct tcc aac acg cca ctg ggg cgc aac ctc tcg act cac cag 1039
 Leu Thr Pro Ser Asn Thr Pro Leu Gly Arg Asn Leu Ser Thr His Gln
 280 285 290
 acc tac ccc gtg gtg gca gct ccg ccc ttt tgg atc tgc agc aag tcg 1087
 Thr Tyr Pro Val Val Ala Ala Pro Pro Phe Trp Ile Cys Ser Lys Ser
 295 300 305
 gct ccg ggg tcc cgc cct tca atg cct ttc ccc atg ctg cct ccg tgt 1135
 Ala Pro Gly Ser Arg Pro Ser Met Pro Phe Pro Met Leu Pro Pro Cys
 310 315 320 325
 acg ggc agt tca cgg gcc agg ccc tcc tct cag ggc gag aga tgg tgg 1183
 Thr Gly Ser Ser Arg Ala Arg Pro Ser Ser Gln Gly Glu Arg Trp Trp
 330 335 340
 ggc cca cgc tgc ccg gat acc cac ccc aca tcc cca cca gcg gac agg 1231
 Gly Pro Arg Cys Pro Asp Thr His Pro Thr Ser Pro Pro Ala Asp Arg
 345 350 355
 gca gct atg cct cct ctg cca tcg cag gca tgg tgg cag gaa gtg aat 1279
 Ala Ala Met Pro Pro Leu Pro Ser Gln Ala Trp Trp Gln Glu Val Asn
 360 365 370
 act ctg gca atg cct atg gcc aca ccc cct act cct cct aca gcg agg 1327
 Thr Leu Ala Met Pro Met Ala Thr Pro Pro Thr Pro Pro Thr Ala Arg
 375 380 385
 cct ggg gct tcc cca act cca gct tgc tgagttcccc atattattac 1374
 Pro Gly Ala Ser Pro Thr Pro Ala Cys
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<211> 398

<212> PRT

<213> NM_013952 PAX8

<400> 44

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Gly Gly Ala Phe Val Asn Gly Arg Pro Leu Pro Glu Val Val Arg Gln
 20 25 30

Arg Ile Val Asp Leu Ala His Gln Gly Val Arg Pro Cys Asp Ile Ser

35

40

45

Arg Gln Leu Arg Val Ser His Gly Cys Val Ser Lys Ile Leu Gly Arg

50

55

60

Tyr Tyr Glu Thr Gly Ser Ile Arg Pro Gly Val Ile Gly Gly Ser Lys

65

70

75

80

Pro Lys Val Ala Thr Pro Lys Val Val Glu Lys Ile Gly Asp Tyr Lys

85

90

95

Arg Gln Asn Pro Thr Met Phe Ala Trp Glu Ile Arg Asp Arg Leu Leu

100

105

110

Ala Glu Gly Val Cys Asp Asn Asp Thr Val Pro Ser Val Ser Ser Ile

115

120

125

Asn Arg Ile Ile Arg Thr Lys Val Gln Gln Pro Phe Asn Leu Pro Met

130

135

140

Asp Ser Cys Val Ala Thr Lys Ser Leu Ser Pro Gly His Thr Leu Ile

145

150

155

160

Pro Ser Ser Ala Val Thr Pro Pro Glu Ser Pro Gln Ser Asp Ser Leu

165

170

175

Gly Ser Thr Tyr Ser Ile Asn Gly Leu Leu Gly Ile Ala Gln Pro Gly

180

185

190

Ser Asp Lys Arg Lys Met Asp Asp Ser Asp Gln Asp Ser Cys Arg Leu

195

200

205

Ser Ile Asp Ser Gln Ser Ser Ser Ser Gly Pro Arg Lys His Leu Arg

210

215

220

Thr Asp Ala Phe Ser Gln His His Leu Glu Pro Leu Glu Cys Pro Phe

225

230

235

240

Glu Arg Gln His Tyr Pro Glu Ala Tyr Ala Ser Pro Ser His Thr Lys

245

250

255

Gly Glu Gln Gly Leu Tyr Pro Leu Pro Leu Leu Asn Ser Thr Leu Asp

260

265

270

Asp Gly Lys Ala Thr Leu Thr Pro Ser Asn Thr Pro Leu Gly Arg Asn

275

280

285

Leu Ser Thr His Gln Thr Tyr Pro Val Val Ala Ala Pro Pro Phe Trp

290

295

300

Ile Cys Ser Lys Ser Ala Pro Gly Ser Arg Pro Ser Met Pro Phe Pro
305 310 315 320

Met Leu Pro Pro Cys Thr Gly Ser Ser Arg Ala Arg Pro Ser Ser Gln
325 330 335

Gly Glu Arg Trp Trp Gly Pro Arg Cys Pro Asp Thr His Pro Thr Ser
340 345 350

Pro Pro Ala Asp Arg Ala Ala Met Pro Pro Leu Pro Ser Gln Ala Trp
355 360 365

Trp Gln Glu Val Asn Thr Leu Ala Met Pro Met Ala Thr Pro Pro Thr
370 375 380

Pro Pro Thr Ala Arg Pro Gly Ala Ser Pro Thr Pro Ala Cys
385 390 395

<210> 45

<211> 326

<212> DNA

<213> AI301558 EST

<400> 45

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gcaggtggtt gcggtcacia agagaaatca tcaagaatgt tcacttggca tgtgtgaaag 180
attcaggggg tctgcagctg tttagtgttg atgcagttgg gtcaaaagag tatcatgtta 240
gtcttctgtg ggttttaggg agggattatg gagcctccct cccacccac tggttttctt 300
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<210> 46

<211> 1534

<212> DNA

<213> NM_018000 FLJ10116

<220>

<221> CDS

<222> (267)..(938)

<223>

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gagaagtcca gcttcaaaag ttacttgcca ctttaagcaag gaacttgtca agagatcatg 1088
gttcatgtta ctgaaaagac ttttaaggatt tgtaagggtta atccatagat tgctgagaac 1148
aatggaaata tttttatttt tacagatttt gcaacttctga attcagggtta aaaactaact 1208
tgtatttagt ctgcttagag gactgtgact tgaaaatttt tatataccaa tgagcttttt 1268
ggtagcgtcc acaatgttta aaatatttca taggcgagat cctgtttctc catttattaa 1328
tgcattgtag accaatttaa ctgctgtgtt tcaggaaaat tcttctagtt ttaataagca 1388
agctaaaagt tttttttttt atatttagtg cttaatcttt gcctcatggt atgtaaaatt 1448
agcctgcaga tttttctctt caattctgta gactctcgca agataaacat tcaaacagtg 1508
aaacaaacaa taaaataaat aaacct 1534

<210> 47

<211> 224

<212> PRT

<213> NM_018000 FLJ10116

<400> 47

Met Gly Leu Arg Asp Trp Leu Arg Thr Val Cys Cys Cys Cys Arg Cys
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Glu Cys Leu Glu Glu Arg Ala Leu Pro Glu Lys Glu Pro Leu Val Ser
20 25 30

Asp Asn Asn Pro Tyr Ser Ser Phe Gly Ala Thr Leu Val Arg Asp Asp
35 40 45

Glu Lys Asn Leu Trp Ser Met Pro His Asp Val Ser His Thr Glu Ala
50 55 60

Asp Asp Asp Arg Thr Leu Tyr Asn Leu Ile Val Ile Arg Asn Gln Gln
65 70 75 80

Ala Lys Asp Ser Glu Glu Trp Gln Lys Leu Asn Tyr Asp Ile His Thr
85 90 95

Leu Arg Gln Val Arg Arg Glu Val Arg Asn Arg Trp Lys Cys Ile Leu
100 105 110

Glu Asp Leu Gly Phe Gln Lys Glu Ala Asp Ser Leu Leu Ser Val Thr
115 120 125

125

Lys Leu Ser Thr Ile Ser Asp Ser Lys Asn Thr Arg Lys Ala Arg Glu
 130 135 140

Met Leu Leu Lys Leu Ala Glu Glu Thr Ser Ile Phe Pro Thr Ser Trp
 145 150 155 160

Glu Leu Ser Glu Arg Tyr Leu Phe Val Val Asp Arg Leu Ile Ala Leu
 165 170 175

Asp Ala Ala Glu Glu Phe Phe Lys Leu Ala Arg Arg Thr Tyr Pro Lys
 180 185 190

Lys Pro Gly Val Pro Cys Leu Ala Asp Gly Gln Lys Glu Leu His Leu
 195 200 205

Trp Gly Asp Leu Ser Cys Arg Leu Ala His Met Gln Gly Val Leu His
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<210> 48

<211> 2385

<212> DNA

<213> NM_144724 FLJ30532

<220>

<221> CDS

<222> (71)..(1441)

<223>

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aaaatcacaa atg tca aat gat gga aga tcc agg aat cgg gac agg cgc 109
 Met Ser Asn Asp Gly Arg Ser Arg Asn Arg Asp Arg Arg
 1 5 10

tac gat gag gtc cca agc gac ctg ccc tat caa gat acc acc ata aga 157
 Tyr Asp Glu Val Pro Ser Asp Leu Pro Tyr Gln Asp Thr Thr Ile Arg
 15 20 25

acc cac cca att ctt cat gac agt gag cgg gca gtg agc gct gat ccc 205
 Thr His Pro Ile Leu His Asp Ser Glu Arg Ala Val Ser Ala Asp Pro
 30 35 40 45

ttg cca cca ccc cct ctc cca tta cag cca cca ttc ggc cca gac ttc 253
 Leu Pro Pro Pro Leu Pro Leu Gln Pro Pro Phe Gly Pro Asp Phe
 50 55 60

tac tca agt gac aca gaa gaa cca gct ata gcg cca gat ctc aaa cca 301
 Tyr Ser Ser Asp Thr Glu Glu Pro Ala Ile Ala Pro Asp Leu Lys Pro
 65 70 75

gta agg cgc ttt gtc cct gac tcc tgg aag aac ttt ttc aga ggg aag 349

Val	Arg	Arg	Phe	Val	Pro	Asp	Ser	Trp	Lys	Asn	Phe	Phe	Arg	Gly	Lys		
	80						85						90				
aaa	aag	gac	ccc	gaa	tgg	gat	aag	ccg	gtg	tct	gat	atc	agg	tac	atc	397	
Lys	Lys	Asp	Pro	Glu	Trp	Asp	Lys	Pro	Val	Ser	Asp	Ile	Arg	Tyr	Ile		
	95						100					105					
tcc	gat	gga	gtg	gag	tgt	tca	cca	cca	gcc	tct	cca	gca	aga	cca	aac	445	
Ser	Asp	Gly	Val	Glu	Cys	Ser	Pro	Pro	Ala	Ser	Pro	Ala	Arg	Pro	Asn		
	110				115					120					125		
cac	cgt	tcg	ccc	ctc	aac	tcc	tgc	aaa	gat	ccc	tac	gga	ggg	tca	gaa	493	
His	Arg	Ser	Pro	Leu	Asn	Ser	Cys	Lys	Asp	Pro	Tyr	Gly	Gly	Ser	Glu		
				130					135					140			
gga	acc	ttt	agt	tcc	cgg	aaa	gag	gct	gac	gca	gtg	ttt	ccc	cgg	gat	541	
Gly	Thr	Phe	Ser	Ser	Arg	Lys	Glu	Ala	Asp	Ala	Val	Phe	Pro	Arg	Asp		
			145					150					155				
ccc	tat	gga	tct	cta	gac	cga	cac	aca	caa	aca	ggt	cga	aca	tac	agt	589	
Pro	Tyr	Gly	Ser	Leu	Asp	Arg	His	Thr	Gln	Thr	Val	Arg	Thr	Tyr	Ser		
		160					165						170				
gag	aag	gtg	gag	gag	tat	aac	ctg	aga	tac	tcc	tac	atg	aag	tcg	tgg	637	
Glu	Lys	Val	Glu	Glu	Tyr	Asn	Leu	Arg	Tyr	Ser	Tyr	Met	Lys	Ser	Trp		
	175					180						185					
gca	ggc	ctg	ctg	aga	ata	ctg	ggt	gtg	gtg	gag	ctg	ctt	ttg	ggg	gcc	685	
Ala	Gly	Leu	Leu	Arg	Ile	Leu	Gly	Val	Val	Glu	Leu	Leu	Leu	Gly	Ala		
	190				195					200					205		
ggt	gtc	ttt	gct	tgt	gtc	aca	gct	tac	att	cac	aag	gac	agt	gag	tgg	733	
Gly	Val	Phe	Ala	Cys	Val	Thr	Ala	Tyr	Ile	His	Lys	Asp	Ser	Glu	Trp		
			210						215					220			
tac	aac	ttg	ttt	gga	tat	tca	caa	ccg	tat	ggc	atg	gga	ggc	gtt	ggt	781	
Tyr	Asn	Leu	Phe	Gly	Tyr	Ser	Gln	Pro	Tyr	Gly	Met	Gly	Gly	Val	Gly		
		225						230					235				
gga	ttg	ggc	agt	atg	tat	ggg	ggc	tat	tac	tac	act	ggc	cct	aag	acc	829	
Gly	Leu	Gly	Ser	Met	Tyr	Gly	Gly	Tyr	Tyr	Tyr	Thr	Gly	Pro	Lys	Thr		
		240					245					250					
cct	ttt	gta	ctc	gtg	ggt	gct	gga	tta	gct	tgg	atc	acc	acc	att	att	877	
Pro	Phe	Val	Leu	Val	Val	Ala	Gly	Leu	Ala	Trp	Ile	Thr	Thr	Ile	Ile		
	255					260					265						
att	ctg	ggt	ctt	ggc	atg	tcc	atg	tat	tac	cgg	acc	att	ctt	ctg	gac	925	
Ile	Leu	Val	Leu	Gly	Met	Ser	Met	Tyr	Tyr	Arg	Thr	Ile	Leu	Leu	Asp		
	270				275					280					285		
tct	aat	tgg	tgg	ccc	cta	act	gaa	ttt	gga	att	aac	ggt	gcc	ttg	ttt	973	
Ser	Asn	Trp	Trp	Pro	Leu	Thr	Glu	Phe	Gly	Ile	Asn	Val	Ala	Leu	Phe		
				290					295				300				
att	ttg	tat	atg	gcc	gca	gcc	ata	gtc	tat	gtg	aat	gat	acc	aac	cga	1021	
Ile	Leu	Tyr	Met	Ala	Ala	Ala	Ile	Val	Tyr	Val	Asn	Asp	Thr	Asn	Arg		
			305					310					315				
ggt	ggc	ctc	tgc	tac	tat	ccg	tta	ttt	aat	aca	cca	gtg	aat	gca	gtg	1069	
Gly	Gly	Leu	Cys	Tyr	Tyr	Pro	Leu	Phe	Asn	Thr	Pro	Val	Asn	Ala	Val		
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ttc	tgc	cgg	gta	gaa	gga	gga	cag	ata	gct	gca	atg	atc	ttc	ctg	ttt	1117	
Phe	Cys	Arg	Val	Glu	Gly	Gln	Ile	Ala	Ala	Met	Ile	Phe	Leu	Phe			
	335					340					345						
gtc	acc	atg	ata	ggt	tat	ctc	att	agt	gct	ttg	ggt	tgc	cta	aag	tta	1165	

Val Thr Met Ile Val Tyr Leu Ile Ser Ala Leu Val Cys Leu Lys Leu
 350 355 360 365
 tgg agg cat gag gca gct cgg aga cat aga gaa tat atg gaa caa cag 1213
 Trp Arg His Glu Ala Ala Arg Arg His Arg Glu Tyr Met Glu Gln Gln
 370 375 380
 gag ata aat gag cca tca ttg tca tgc aaa agg aaa atg tgt gaa atg 1261
 Glu Ile Asn Glu Pro Ser Leu Ser Ser Lys Arg Lys Met Cys Glu Met
 385 390 395
 gcc acc agt ggt gac aga caa aga gac tca gaa gtt aat ttc aag gaa 1309
 Ala Thr Ser Gly Asp Arg Gln Arg Asp Ser Glu Val Asn Phe Lys Glu
 400 405 410
 ctg aga aca gca aaa atg aaa cct gaa cta ctg agt gga cac atc ccc 1357
 Leu Arg Thr Ala Lys Met Lys Pro Glu Leu Leu Ser Gly His Ile Pro
 415 420 425
 cca cgc cca gct aat ttt ttt gta ttt tta gta gag atg ggg ttt cac 1405
 Pro Arg Pro Ala Asn Phe Phe Val Phe Leu Val Glu Met Gly Phe His
 430 435 440 445
 cgt gtt agc cag gat gat ctc gat ctc ctg acc tca tgatccaccc 1451
 Arg Val Ser Gln Asp Asp Leu Asp Leu Thr Ser
 450 455
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 tattttctgtt agtatgaaca atagactgcc ttaacaaagt ttttttttaa acaaaatcgt 1991
 tcttggttga ttttattcag cagcatctat catgtagata aattcccagg ttagcatta 2051
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 tccatggctt ttaggctgt gctgtgtctg aaggggtaac acctagggaa acatgaggcc 2291
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<211> 457

<212> PRT

<213> NM_144724 FLJ30532

<400> 49

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Ile Leu His Asp Ser Glu Arg Ala Val Ser Ala Asp Pro Leu Pro Pro
35 40 45

Pro Pro Leu Pro Leu Gln Pro Pro Phe Gly Pro Asp Phe Tyr Ser Ser
50 55 60

Asp Thr Glu Glu Pro Ala Ile Ala Pro Asp Leu Lys Pro Val Arg Arg
65 70 75 80

Phe Val Pro Asp Ser Trp Lys Asn Phe Phe Arg Gly Lys Lys Lys Asp
85 90 95

Pro Glu Trp Asp Lys Pro Val Ser Asp Ile Arg Tyr Ile Ser Asp Gly
100 105 110

Val Glu Cys Ser Pro Pro Ala Ser Pro Ala Arg Pro Asn His Arg Ser
115 120 125

Pro Leu Asn Ser Cys Lys Asp Pro Tyr Gly Gly Ser Glu Gly Thr Phe
130 135 140

Ser Ser Arg Lys Glu Ala Asp Ala Val Phe Pro Arg Asp Pro Tyr Gly
145 150 155 160

Ser Leu Asp Arg His Thr Gln Thr Val Arg Thr Tyr Ser Glu Lys Val
165 170 175

Glu Glu Tyr Asn Leu Arg Tyr Ser Tyr Met Lys Ser Trp Ala Gly Leu
180 185 190

Leu Arg Ile Leu Gly Val Val Glu Leu Leu Leu Gly Ala Gly Val Phe
195 200 205

Ala Cys Val Thr Ala Tyr Ile His Lys Asp Ser Glu Trp Tyr Asn Leu
210 215 220

Phe Gly Tyr Ser Gln Pro Tyr Gly Met Gly Gly Val Gly Gly Leu Gly
225 230 235 240

Ser Met Tyr Gly Gly Tyr Tyr Tyr Thr Gly Pro Lys Thr Pro Phe Val
245 250 255

Leu Val Val Ala Gly Leu Ala Trp Ile Thr Thr Ile Ile Ile Leu Val
260 265 270

Leu Gly Met Ser Met Tyr Tyr Arg Thr Ile Leu Leu Asp Ser Asn Trp
275 280 285

Trp Pro Leu Thr Glu Phe Gly Ile Asn Val Ala Leu Phe Ile Leu Tyr
290 295 300

Met Ala Ala Ala Ile Val Tyr Val Asn Asp Thr Asn Arg Gly Gly Leu
305 310 315 320

Cys Tyr Tyr Pro Leu Phe Asn Thr Pro Val Asn Ala Val Phe Cys Arg
325 330 335

Val Glu Gly Gly Gln Ile Ala Ala Met Ile Phe Leu Phe Val Thr Met
340 345 350

Ile Val Tyr Leu Ile Ser Ala Leu Val Cys Leu Lys Leu Trp Arg His
355 360 365

Glu Ala Ala Arg Arg His Arg Glu Tyr Met Glu Gln Gln Glu Ile Asn
370 375 380

Glu Pro Ser Leu Ser Ser Lys Arg Lys Met Cys Glu Met Ala Thr Ser
385 390 395 400

Gly Asp Arg Gln Arg Asp Ser Glu Val Asn Phe Lys Glu Leu Arg Thr
405 410 415

Ala Lys Met Lys Pro Glu Leu Leu Ser Gly His Ile Pro Pro Arg Pro
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Ala Asn Phe Phe Val Phe Leu Val Glu Met Gly Phe His Arg Val Ser
435 440 445

Gln Asp Asp Leu Asp Leu Leu Thr Ser
450 455

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<211> 2280

<212> DNA

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<221> CDS

<222> (64)..(2133)

<223>

<400> 50

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 Met Ala Pro Trp Pro Glu Leu Gly Asp Ala Gln Pro Asn Pro Asp
 1 5 10 15
 aag tac ctc gaa ggg gcc gca ggt cag cag ccc act gcc cct gat aaa 156
 Lys Tyr Leu Glu Gly Ala Ala Gly Gln Gln Pro Thr Ala Pro Asp Lys
 20 25 30
 agc aaa gag acc aac aaa aca gat aac act gag gca cct gta acc aag 204
 Ser Lys Glu Thr Asn Lys Thr Asp Asn Thr Glu Ala Pro Val Thr Lys
 35 40 45
 att gaa ctt ctg ccg tcc tac tcc acg gct aca ctg ata gat gag ccc 252
 Ile Glu Leu Leu Pro Ser Tyr Ser Thr Ala Thr Leu Ile Asp Glu Pro
 50 55 60
 act gag gtg gat gac ccc tgg aac cta ccc act ctt cag gac tcg ggg 300
 Thr Glu Val Asp Asp Pro Trp Asn Leu Pro Thr Leu Gln Asp Ser Gly
 65 70 75
 atc aag tgg tca gag aga gac acc aaa ggg aag att ctc tgt ttc ttc 348
 Ile Lys Trp Ser Glu Arg Asp Thr Lys Gly Lys Ile Leu Cys Phe Phe
 80 85 90 95
 caa ggg att ggg aga ttg att tta ctt ctc gga ttt ctc tac ttt ttc 396
 Gln Gly Ile Gly Arg Leu Ile Leu Leu Leu Gly Phe Leu Tyr Phe Phe
 100 105 110
 gtg tgc tcc ctg gat att ctt agt agc gcc ttc cag ctg gtt gga gga 444
 Val Cys Ser Leu Asp Ile Leu Ser Ser Ala Phe Gln Leu Val Gly Gly
 115 120 125
 aaa atg gca gga cag ttc ttc agc aac agc tct att atg tcc aac cct 492
 Lys Met Ala Gly Gln Phe Phe Ser Asn Ser Ser Ile Met Ser Asn Pro
 130 135 140
 ttg ttg ggg ctg gtg atc ggg gtg ctg gtg acc gtc ttg gtg cag agc 540
 Leu Leu Gly Leu Val Ile Gly Val Leu Val Thr Val Leu Val Gln Ser
 145 150 155
 tcc agc acc tca acg tcc atc gtt gtc agc atg gtg tcc tct tca ttg 588
 Ser Ser Thr Ser Thr Ser Ile Val Val Ser Met Val Ser Ser Ser Leu
 160 165 170 175
 ctc act gtt cgg gct gcc atc ccc att atc atg ggg gcc aac att gga 636
 Leu Thr Val Arg Ala Ala Ile Pro Ile Ile Met Gly Ala Asn Ile Gly
 180 185 190
 acg tca atc acc aac act att gtt gcg ctc atg cag gtg gga gat cgg 684
 Thr Ser Ile Thr Asn Thr Ile Val Ala Leu Met Gln Val Gly Asp Arg
 195 200 205
 agt gag ttc aga aga gct ttt gca gga gcc act gtc cat gac ttc ttc 732
 Ser Glu Phe Arg Arg Ala Phe Ala Gly Ala Thr Val His Asp Phe Phe
 210 215 220
 aac tgg ctg tcc gtg ttg gtg ctc ttg ccc gtg gag gtg gcc acc cat 780
 Asn Trp Leu Ser Val Leu Val Leu Leu Pro Val Glu Val Ala Thr His
 225 230 235

tac ctc gag atc ata acc cag ctt ata gtg gag agc ttc cac ttc aag Tyr Leu Glu Ile Ile Thr Gln Leu Ile Val Glu Ser Phe His Phe Lys 240 245 250 255	828
aat gga gaa gat gcc cca gat ctt ctg aaa gtc atc act aag ccc ttc Asn Gly Glu Asp Ala Pro Asp Leu Leu Lys Val Ile Thr Lys Pro Phe 260 265 270	876
aca aag ctc att gtc cag ctg gat aaa aaa gtt atc agc caa att gca Thr Lys Leu Ile Val Gln Leu Asp Lys Lys Val Ile Ser Gln Ile Ala 275 280 285	924
atg aac gat gaa aaa gcg aaa aac aag agt ctt gtc aag att tgg tgc Met Asn Asp Glu Lys Ala Lys Asn Lys Ser Leu Val Lys Ile Trp Cys 290 295 300	972
aaa act ttt acc aac aag acc cag att aac gtc act gtt ccc tcg act Lys Thr Phe Thr Asn Lys Thr Gln Ile Asn Val Thr Val Pro Ser Thr 305 310 315	1020
gct aac tgc acc tcc cct tcc ctc tgt tgg acg gat ggc atc caa aac Ala Asn Cys Thr Ser Pro Ser Leu Cys Trp Thr Asp Gly Ile Gln Asn 320 325 330 335	1068
tgg acc atg aag aat gtg acc tac aag gag aac atc gcc aaa tgc cag Trp Thr Met Lys Asn Val Thr Tyr Lys Glu Asn Ile Ala Lys Cys Gln 340 345 350	1116
cat atc ttt gtg aat ttc cac ctc ccg gat ctt gct gtg ggc acc atc His Ile Phe Val Asn Phe His Leu Pro Asp Leu Ala Val Gly Thr Ile 355 360 365	1164
ttg ctc ata ctc tcc ctg ctg gtc ctc tgt ggt tgc ctg atc atg att Leu Leu Ile Leu Ser Leu Leu Val Leu Cys Gly Cys Leu Ile Met Ile 370 375 380	1212
gtc aag atc ctg ggc tct gtg ctc aag ggg cag gtc gcc act gtc atc Val Lys Ile Leu Gly Ser Val Leu Lys Gly Gln Val Ala Thr Val Ile 385 390 395	1260
aag aag acc atc aac act gat ttc ccc ttt ccc ttt gca tgg ttg act Lys Lys Thr Ile Asn Thr Asp Phe Pro Phe Ala Trp Leu Thr 400 405 410 415	1308
ggc tac ctg gcc atc ctc gtc ggg gca ggc atg acc ttc atc gta cag Gly Tyr Leu Ala Ile Leu Val Gly Ala Gly Met Thr Phe Ile Val Gln 420 425 430	1356
agc agc tct gtg ttc acg tcg gcc ttg acc ccc ctg att gga atc ggc Ser Ser Ser Val Phe Thr Ser Ala Leu Thr Pro Leu Ile Gly Ile Gly 435 440 445	1404
gtg ata acc att gag agg gct tat cca ctc acg ctg ggc tcc aac atc Val Ile Thr Ile Glu Arg Ala Tyr Pro Leu Thr Leu Gly Ser Asn Ile 450 455 460	1452
ggc acc acc acc acc gcc atc ctg gcc gcc tta gcc agc cct ggc aat Gly Thr Thr Thr Thr Ala Ile Leu Ala Ala Leu Ala Ser Pro Gly Asn 465 470 475	1500
gca ttg agg agt tca ctc cag atc gcc ctg tgc cac ttt ttc ttc aac Ala Leu Arg Ser Ser Leu Gln Ile Ala Leu Cys His Phe Phe Phe Asn 480 485 490 495	1548
atc tcc ggc atc ttg ctg tgg tac ccg atc ccg ttc act cgc ctg ccc Ile Ser Gly Ile Leu Leu Trp Tyr Pro Ile Pro Phe Thr Arg Leu Pro 500 505 510	1596

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 Ile Arg Met Ala Lys Gly Leu Gly Asn Ile Ser Ala Lys Tyr Arg Trp
 515 520 525
 ttc gcc gtc ttc tac ctg atc atc ttc ttc ttc ctg atc ccg ctg acg 1692
 Phe Ala Val Phe Tyr Leu Ile Ile Phe Phe Phe Leu Ile Pro Leu Thr
 530 535 540
 gtg ttt ggc ctc tcg ctg gcc ggc tgg cgg gtg ctg gtt ggt gtc ggg 1740
 Val Phe Gly Leu Ser Leu Ala Gly Trp Arg Val Leu Val Gly Val Gly
 545 550 555
 gtt ccc gtc gtc ttc atc atc atc ctg gta ctg tgc ctc cga ctc ctg 1788
 Val Pro Val Val Phe Ile Ile Ile Leu Val Leu Cys Leu Arg Leu Leu
 560 565 570 575
 cag tct cgc tgc cca cgc gtc ctg ccg aag aaa ctc cag aac tgg aac 1836
 Gln Ser Arg Cys Pro Arg Val Leu Pro Lys Lys Leu Gln Asn Trp Asn
 580 585 590
 ttc ctg ccg ctg tgg atg cgc tcg ctg aag ccc tgg gat gcc gtc gtc 1884
 Phe Leu Pro Leu Trp Met Arg Ser Leu Lys Pro Trp Asp Ala Val Val
 595 600 605
 tcc aag ttc acc ggc tgc ttc cag atg cgc tgc tgc tac tgc tgc cgc 1932
 Ser Lys Phe Thr Gly Cys Phe Gln Met Arg Cys Cys Tyr Cys Cys Arg
 610 615 620
 gtg tgc tgc cgc gcg tgc tgc ttg ctg tgt ggc tgc ccc aag tgc tgc 1980
 Val Cys Cys Arg Ala Cys Cys Leu Leu Cys Gly Cys Pro Lys Cys Cys
 625 630 635
 cgc tgc agc aag tgc tgc gag gac ttg gag gag gcg cag gag ggg cag 2028
 Arg Cys Ser Lys Cys Cys Glu Asp Leu Glu Glu Ala Gln Glu Gly Gln
 640 645 650 655
 gat gtc cct gtc aag gct cct gag acc ttt gat aac ata acc att agc 2076
 Asp Val Pro Val Lys Ala Pro Glu Thr Phe Asp Asn Ile Thr Ile Ser
 660 665 670
 aga gag gct cag ggt gag gtc cct gcc tcg gac tca aag acc gaa tgc 2124
 Arg Glu Ala Gln Gly Glu Val Pro Ala Ser Asp Ser Lys Thr Glu Cys
 675 680 685
 acg gcc ttg taggggacgc ccagattgt cagggatggg gggatggtcc 2173
 Thr Ala Leu
 690
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<211> 690

<212> PRT

<213> NM_006424 SLC34A2

<400> 51

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Tyr Leu Glu Gly Ala Ala Gly Gln Gln Pro Thr Ala Pro Asp Lys Ser
20 25 30

Lys Glu Thr Asn Lys Thr Asp Asn Thr Glu Ala Pro Val Thr Lys Ile
35 40 45

Glu Leu Leu Pro Ser Tyr Ser Thr Ala Thr Leu Ile Asp Glu Pro Thr
50 55 60

Glu Val Asp Asp Pro Trp Asn Leu Pro Thr Leu Gln Asp Ser Gly Ile
65 70 75 80

Lys Trp Ser Glu Arg Asp Thr Lys Gly Lys Ile Leu Cys Phe Phe Gln
85 90 95

Gly Ile Gly Arg Leu Ile Leu Leu Leu Gly Phe Leu Tyr Phe Phe Val
100 105 110

Cys Ser Leu Asp Ile Leu Ser Ser Ala Phe Gln Leu Val Gly Gly Lys
115 120 125

Met Ala Gly Gln Phe Phe Ser Asn Ser Ser Ile Met Ser Asn Pro Leu
130 135 140

Leu Gly Leu Val Ile Gly Val Leu Val Thr Val Leu Val Gln Ser Ser
145 150 155 160

Ser Thr Ser Thr Ser Ile Val Val Ser Met Val Ser Ser Ser Leu Leu
165 170 175

Thr Val Arg Ala Ala Ile Pro Ile Ile Met Gly Ala Asn Ile Gly Thr
180 185 190

Ser Ile Thr Asn Thr Ile Val Ala Leu Met Gln Val Gly Asp Arg Ser
195 200 205

Glu Phe Arg Arg Ala Phe Ala Gly Ala Thr Val His Asp Phe Phe Asn
210 215 220

Trp Leu Ser Val Leu Val Leu Leu Pro Val Glu Val Ala Thr His Tyr
225 230 235 240

Leu Glu Ile Ile Thr Gln Leu Ile Val Glu Ser Phe His Phe Lys Asn
245 250 255

Gly Glu Asp Ala Pro Asp Leu Leu Lys Val Ile Thr Lys Pro Phe Thr
260 265 270

Lys Leu Ile Val Gln Leu Asp Lys Lys Val Ile Ser Gln Ile Ala Met

275	280	285
Asn Asp Glu Lys Ala Lys Asn Lys Ser Leu Val Lys Ile Trp Cys Lys		
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Thr Phe Thr Asn Lys Thr Gln Ile Asn Val Thr Val Pro Ser Thr Ala		
305	310	315 320
Asn Cys Thr Ser Pro Ser Leu Cys Trp Thr Asp Gly Ile Gln Asn Trp		
	325	330 335
Thr Met Lys Asn Val Thr Tyr Lys Glu Asn Ile Ala Lys Cys Gln His		
	340	345 350
Ile Phe Val Asn Phe His Leu Pro Asp Leu Ala Val Gly Thr Ile Leu		
	355	360 365
Leu Ile Leu Ser Leu Leu Val Leu Cys Gly Cys Leu Ile Met Ile Val		
	370	375 380
Lys Ile Leu Gly Ser Val Leu Lys Gly Gln Val Ala Thr Val Ile Lys		
	385	390 395 400
Lys Thr Ile Asn Thr Asp Phe Pro Phe Pro Phe Ala Trp Leu Thr Gly		
	405	410 415
Tyr Leu Ala Ile Leu Val Gly Ala Gly Met Thr Phe Ile Val Gln Ser		
	420	425 430
Ser Ser Val Phe Thr Ser Ala Leu Thr Pro Leu Ile Gly Ile Gly Val		
	435	440 445
Ile Thr Ile Glu Arg Ala Tyr Pro Leu Thr Leu Gly Ser Asn Ile Gly		
	450	455 460
Thr Thr Thr Thr Ala Ile Leu Ala Ala Leu Ala Ser Pro Gly Asn Ala		
	465	470 475 480
Leu Arg Ser Ser Leu Gln Ile Ala Leu Cys His Phe Phe Phe Asn Ile		
	485	490 495
Ser Gly Ile Leu Leu Trp Tyr Pro Ile Pro Phe Thr Arg Leu Pro Ile		
	500	505 510
Arg Met Ala Lys Gly Leu Gly Asn Ile Ser Ala Lys Tyr Arg Trp Phe		
	515	520 525
Ala Val Phe Tyr Leu Ile Ile Phe Phe Phe Leu Ile Pro Leu Thr Val		
	530	535 540
Phe Gly Leu Ser Leu Ala Gly Trp Arg Val Leu Val Gly Val Gly Val		

545 550 555 560
 Pro Val Val Phe Ile Ile Ile Leu Val Leu Cys Leu Arg Leu Leu Gln
 565 570 575
 Ser Arg Cys Pro Arg Val Leu Pro Lys Lys Leu Gln Asn Trp Asn Phe
 580 585 590
 Leu Pro Leu Trp Met Arg Ser Leu Lys Pro Trp Asp Ala Val Val Ser
 595 600 605
 Lys Phe Thr Gly Cys Phe Gln Met Arg Cys Cys Tyr Cys Cys Arg Val
 610 615 620
 Cys Cys Arg Ala Cys Cys Leu Leu Cys Gly Cys Pro Lys Cys Cys Arg
 625 630 635 640
 Cys Ser Lys Cys Cys Glu Asp Leu Glu Glu Ala Gln Glu Gly Gln Asp
 645 650 655
 Val Pro Val Lys Ala Pro Glu Thr Phe Asp Asn Ile Thr Ile Ser Arg
 660 665 670
 Glu Ala Gln Gly Glu Val Pro Ala Ser Asp Ser Lys Thr Glu Cys Thr
 675 680 685
 Ala Leu
 690

<210> 52

<211> 529

<212> DNA

<213> AW959311, DKFZp434J037, EST

<220>

<221> misc_feature

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<223> the residue at position 393 is A, T C or G

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 caaggggccc agcctcctct ggactccacc ttggacctca gtgactcaga acttctgcct 180
 ctaagctgct ctaaagtcca gactatggat gtgttctcta ggccttcagg actotagaat 240

gtccatattt atttttatgt tcttggttt gtgttttagg aaaagtgaat cttgctgttt 300
 tcaataatgt gaatgctatg ttctgggaaa atccactatg acatctaagt tttgtgtaca 360
 gagagatatt tttgcaacta tttccacctt ctncacacac ccccccacact ccactccaca 420
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<210> 53

<211> 2100

<212> DNA

<213> AF111713 JAM1, junctional adhesion molecule 1

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<221> CDS

<222> (287)..(1183)

<223>

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 gctgaaggag tccttcggcg gctgttgtgt cgggagcctg atcgcg atg ggg aca 295
 Met Gly Thr
 1
 aag gcg caa gtc gag agg aaa ctg ttg tgc ctc ttc ata ttg gcg atc 343
 Lys Ala Gln Val Glu Arg Lys Leu Leu Cys Leu Phe Ile Leu Ala Ile
 5 10 15
 ctg ttg tgc tcc ctg gca ttg ggc agt gtt aca gtg cac tct tct gaa 391
 Leu Leu Cys Ser Leu Ala Leu Gly Ser Val Thr Val His Ser Ser Glu
 20 25 30 35
 cct gaa gtc aga att cct gag aat aat cct gtg aag ttg tcc tgt gcc 439
 Pro Glu Val Arg Ile Pro Glu Asn Asn Pro Val Lys Leu Ser Cys Ala
 40 45 50
 tac tcg ggc ttt tct tct ccc cgt gtg gag tgg aag ttt gac caa gga 487
 Tyr Ser Gly Phe Ser Ser Pro Arg Val Glu Trp Lys Phe Asp Gln Gly
 55 60 65
 gac acc acc aga ctc gtt tgc tat aat aac aag atc aca gct tcc tat 535
 Asp Thr Thr Arg Leu Val Cys Tyr Asn Asn Lys Ile Thr Ala Ser Tyr
 70 75 80
 gag gac cgg gtg acc ttc ttg cca act ggt atc acc ttc aag tcc gtg 583
 Glu Asp Arg Val Thr Phe Leu Pro Thr Gly Ile Thr Phe Lys Ser Val
 85 90 95

aca cgg gaa gac act ggg aca tac act tgt atg gtc tct gag gaa ggc Thr Arg Glu Asp Thr Gly Thr Tyr Thr Cys Met Val Ser Glu Glu Gly 100 105 110 115	631
ggc aac agc tat ggg gag gtc aag gtc aag ctc atc gtg ctt gtg cct Gly Asn Ser Tyr Gly Glu Val Lys Val Lys Leu Ile Val Leu Val Pro 120 125 130	679
cca tcc aag cct aca gtt aac atc ccc tcc tct gcc acc att ggg aac Pro Ser Lys Pro Thr Val Asn Ile Pro Ser Ser Ala Thr Ile Gly Asn 135 140 145	727
cgg gca gtg ctg aca tgc tca gaa caa gat ggt tcc cca cct tct gaa Arg Ala Val Leu Thr Cys Ser Glu Gln Asp Gly Ser Pro Pro Ser Glu 150 155 160	775
tac acc tgg ttc aaa gat ggg ata gtg atg cct acg aat ccc aaa agc Tyr Thr Trp Phe Lys Asp Gly Ile Val Met Pro Thr Asn Pro Lys Ser 165 170 175	823
acc cgt gcc ttc agc aac tct tcc tat gtc ctg aat ccc aca aca gga Thr Arg Ala Phe Ser Asn Ser Ser Tyr Val Leu Asn Pro Thr Thr Gly 180 185 190 195	871
gag ctg gtc ttt gat ccc ctg tca gcc tct gat act gga gaa tac agc Glu Leu Val Phe Asp Pro Leu Ser Ala Ser Asp Thr Gly Glu Tyr Ser 200 205 210	919
tgt gag gca cgg aat ggg tat ggg aca ccc atg act tca aat gct gtg Cys Glu Ala Arg Asn Gly Tyr Gly Thr Pro Met Thr Ser Asn Ala Val 215 220 225	967
cgc atg gaa gct gtg gag cgg aat gtg ggg gtc atc gtg gca gcc gtc Arg Met Glu Ala Val Glu Arg Asn Val Gly Val Ile Val Ala Ala Val 230 235 240	1015
ctt gta acc ctg att ctc ctg gga atc ttg gtt ttt ggc atc tgg ttt Leu Val Thr Leu Ile Leu Leu Gly Ile Leu Val Phe Gly Ile Trp Phe 245 250 255	1063
gcc tat agc cga ggc cac ttt gac aga aca aag aaa ggg act tcg agt Ala Tyr Ser Arg Gly His Phe Asp Arg Thr Lys Lys Gly Thr Ser Ser 260 265 270 275	1111
aag aag gtg att tac agc cag cct agt gcc cga agt gaa gga gaa ttc Lys Lys Val Ile Tyr Ser Gln Pro Ser Ala Arg Ser Glu Gly Glu Phe 280 285 290	1159
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tgccattatt gtcttctaca cccacaggg cccctactt cttcggatgt gtttttaata	1333
atgtcagcta tgtgccccat cctccttcac gccctccctc cctttctac cactgctgag	1393
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tctgggctct ttccttgtgt actgacgacc agggccagct gttctagagt ggggaattaga	1633
ggctagagcg gctgaaatgg ttgtttgtg atgacactgg ggtccttcca tctctggggc	1693

ccactctctt ctgtcttccc atgggaagtg ccactgggat ccctctgccc tgcctcctg 1753
 aatacaagct gactgacatt gactgtgtct gtggaaaatg ggagctcttg ttgtggagag 1813
 catagtaaatt tttagagaa ctgaagcga aaaggattta aaaccgctgc tctaaagaaa 1873
 agaaaactgg aggtggggcg cagtgggtca cgctgtaat cccagaggct gaggcaggcg 1933
 gatcacctga ggtcgggagt tcgggatcag cctgaccaac atggagaaac cctgctggaa 1993
 atacagagtt agccaggcat ggtggtgcat gcctgtagtc ccagctgctc aggagcctgg 2053
 caacaagagc aaaactccag ctcaaaaaaa aaaaaaaaaa aaaaaaa 2100

<210> 54

<211> 299

<212> PRT

<213> AF111713 JAM1, junctional adhesion molecule 1

<400> 54

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Ser Ser Glu Pro Glu Val Arg Ile Pro Glu Asn Asn Pro Val Lys Leu
 35 40 45

Ser Cys Ala Tyr Ser Gly Phe Ser Ser Pro Arg Val Glu Trp Lys Phe
 50 55 60

Asp Gln Gly Asp Thr Thr Arg Leu Val Cys Tyr Asn Asn Lys Ile Thr
 65 70 75 80

Ala Ser Tyr Glu Asp Arg Val Thr Phe Leu Pro Thr Gly Ile Thr Phe
 85 90 95

Lys Ser Val Thr Arg Glu Asp Thr Gly Thr Tyr Thr Cys Met Val Ser
 100 105 110

Glu Glu Gly Gly Asn Ser Tyr Gly Glu Val Lys Val Lys Leu Ile Val
 115 120 125

Leu Val Pro Pro Ser Lys Pro Thr Val Asn Ile Pro Ser Ser Ala Thr
 130 135 140

Ile Gly Asn Arg Ala Val Leu Thr Cys Ser Glu Gln Asp Gly Ser Pro
 145 150 155 160

Pro Ser Glu Tyr Thr Trp Phe Lys Asp Gly Ile Val Met Pro Thr Asn
165 170 175

Pro Lys Ser Thr Arg Ala Phe Ser Asn Ser Ser Tyr Val Leu Asn Pro
180 185 190

Thr Thr Gly Glu Leu Val Phe Asp Pro Leu Ser Ala Ser Asp Thr Gly
195 200 205

Glu Tyr Ser Cys Glu Ala Arg Asn Gly Tyr Gly Thr Pro Met Thr Ser
210 215 220

Asn Ala Val Arg Met Glu Ala Val Glu Arg Asn Val Gly Val Ile Val
225 230 235 240

Ala Ala Val Leu Val Thr Leu Ile Leu Leu Gly Ile Leu Val Phe Gly
245 250 255

Ile Trp Phe Ala Tyr Ser Arg Gly His Phe Asp Arg Thr Lys Lys Gly
260 265 270

Thr Ser Ser Lys Lys Val Ile Tyr Ser Gln Pro Ser Ala Arg Ser Glu
275 280 285

Gly Glu Phe Lys Gln Thr Ser Ser Phe Leu Val
290 295

<210> 55

<211> 2154

<212> DNA

<213> NM_006636 MTHFD2, methylene tetrahydrofolate

<220>

<221> CDS

<222> (77)..(1108)

<223>

<400> 55

atataaccgc gtggcccgcg cgcgcgcttc cctcccggcg cagtcaccgg cgcggtctat 60

ggctgcgact tctcta atg tct gct ttg gct gcc cgg ctg ctg cag ccc gcg 112
Met Ser Ala Leu Ala Ala Arg Leu Leu Gln Pro Ala
1 5 10

cac agc tgc tcc ctt cgc ctt cgc cct ttc cac ctc gcg gca gtt cga 160
His Ser Cys Ser Leu Arg Leu Arg Pro Phe His Leu Ala Ala Val Arg
15 20 25

aat gaa gct gtt gtc att tct gga agg aaa ctg gcc cag cag atc aag Asn Glu Ala Val Val Ile Ser Gly Arg Lys Leu Ala Gln Gln Ile Lys 30 35 40	208
cag gaa gtg cgg cag gag gta gaa gag tgg gtg gcc tca ggc aac aaa Gln Glu Val Arg Gln Glu Val Glu Glu Trp Val Ala Ser Gly Asn Lys 45 50 55 60	256
cgg cca cac ctg agt gtg atc ctg gtt ggc gag aat cct gca agt cac Arg Pro His Leu Ser Val Ile Leu Val Gly Glu Asn Pro Ala Ser His 65 70 75	304
tcc tat gtc ctc aac aaa acc agg gca gct gca gtt gtg gga atc aac Ser Tyr Val Leu Asn Lys Thr Arg Ala Ala Val Val Gly Ile Asn 80 85 90	352
agt gag aca att atg aaa cca gct tca att tca gag gaa gaa ttg ttg Ser Glu Thr Ile Met Lys Pro Ala Ser Ile Ser Glu Glu Glu Leu Leu 95 100 105	400
aat tta atc aat aaa ctg aat aat gat gat aat gta gat ggc ctc ctt Asn Leu Ile Asn Lys Leu Asn Asn Asp Asp Asn Val Asp Gly Leu Leu 110 115 120	448
gtt cag ttg cct ctt cca gag cat att gat gag aga agg atc tgc aat Val Gln Leu Pro Leu Pro Glu His Ile Asp Glu Arg Arg Ile Cys Asn 125 130 135 140	496
gct gtt tct cca gac aag gat gtt gat ggc ttt cat gta att aat gta Ala Val Ser Pro Asp Lys Asp Val Asp Gly Phe His Val Ile Asn Val 145 150 155	544
gga cga atg tgt ttg gat cag tat tcc atg tta ccg gct act cca tgg Gly Arg Met Cys Leu Asp Gln Tyr Ser Met Leu Pro Ala Thr Pro Trp 160 165 170	592
ggt gtg tgg gaa ata atc aag cga act ggc att cca acc cta ggg aag Gly Val Trp Glu Ile Ile Lys Arg Thr Gly Ile Pro Thr Leu Gly Lys 175 180 185	640
aat gtg gtt gtg gct gga agg tca aaa aac gtt gga atg ccc att gca Asn Val Val Val Ala Gly Arg Ser Lys Asn Val Gly Met Pro Ile Ala 190 195 200	688
atg tta ctg cac aca gat ggg gcg cat gaa cgt ccc gga ggt gat gcc Met Leu Leu His Thr Asp Gly Ala His Glu Arg Pro Gly Gly Asp Ala 205 210 215 220	736
act gtt aca ata tct cat cga tat act ccc aaa gag cag ttg aag aaa Thr Val Thr Ile Ser His Arg Tyr Thr Pro Lys Glu Gln Leu Lys Lys 225 230 235	784
cat aca att ctt gca gat att gta ata tct gct gca ggt att cca aat His Thr Ile Leu Ala Asp Ile Val Ile Ser Ala Ala Gly Ile Pro Asn 240 245 250	832
ctg atc aca gca gat atg atc aag gaa gga gca gca gtc att gat gtg Leu Ile Thr Ala Asp Met Ile Lys Glu Gly Ala Ala Val Ile Asp Val 255 260 265	880
gga ata aat aga gtt cac gat cct gta act gcc aaa ccc aag ttg gtt Gly Ile Asn Arg Val His Asp Pro Val Thr Ala Lys Pro Lys Leu Val 270 275 280	928
gga gat gtg gat ttt gaa gga gtc aga caa aaa gct ggg tat atc act Gly Asp Val Asp Phe Glu Gly Val Arg Gln Lys Ala Gly Tyr Ile Thr 285 290 295 300	976

cca gtt cct gga ggt gtt ggc ccc atg aca gtg gca atg cta atg aag 1024
 Pro Val Pro Gly Gly Val Gly Pro Met Thr Val Ala Met Leu Met Lys
 305 310 315

aat acc att att gct gca aaa aag gtg ctg agg ctt gaa gag cga gaa 1072
 Asn Thr Ile Ile Ala Ala Lys Lys Val Leu Arg Leu Glu Glu Arg Glu
 320 325 330

gtg ctg aag tct aaa gag ctt ggg gta gcc act aat taactactgt 1118
 Val Leu Lys Ser Lys Glu Leu Gly Val Ala Thr Asn
 335 340

gtcttctgtg tcacaaacag cactccaggc cagctcaaga agcaaagcag gccaatagaa 1178

atgcaatatt ttttaatttat tctactgaaa tgggttaaaa tgatgccttg tatattattga 1238

aagcttaaatt ggggtgggtgt ttctgcacat acctctgcag tacctcacca gggagcattc 1298

cagtatcatg caggggtcctg tgatctagcc aggagcagcc attaacctag tgattaatat 1358

gggagacatt accatatgga ggatggatgc ttcactttgt caagcacctc agttacacat 1418

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aggtagcaga ccttttgagt tcaactgac aaaccaaagg aaaagtgttg ctagagaaaa 1538

ttggggaaaa ggtgaaaaag aaaaaatggt agtaattgag cagaaaaaaa ttaatttata 1598

tatgtattga ttggcaacca gatttatcta agtagaactg aattggctag gaaaaaagaa 1658

aaactgcatg ttaatcattt tcctaagctg tccttttgag gcttagtcag tttattggga 1718

aaatgtttag gattattcct tgctattagt actcatttta tgtatgttac ctttcagtaa 1778

gttctcccca ttttagtttt ctaggactga aaggattcct ttctacatta tacatgtgtg 1838

ttgtcatatt tggcttttgc tatatacttt aacttcattg ttaaattttt gtattgtata 1898

gtttcttttg tgtatcttaa aacctatttt tgaaaaacaa acttggttg ataatacattt 1958

gggcagcttg ggtaagtacg caacttactt ttccaccaa gaactgtcag cagctgcctg 2018

cttttctgtg atgtatgtat cctgttgact ttccagaaa ttttttaaga gtttgagtta 2078

ctattgaatt taatcagact ttctgattaa aggggtttct ttctttttta ataaaacaca 2138

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<210> 56

<211> 344

<212> PRT

<213> NM_006636 MTHFD2, methylene tetrahydrofolate

<400> 56

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Leu Arg Leu Arg Pro Phe His Leu Ala Ala Val Arg Asn Glu Ala Val
 20 25 30

Val Ile Ser Gly Arg Lys Leu Ala Gln Gln Ile Lys Gln Glu Val Arg
 35 40 45
 Gln Glu Val Glu Glu Trp Val Ala Ser Gly Asn Lys Arg Pro His Leu
 50 55 60
 Ser Val Ile Leu Val Gly Glu Asn Pro Ala Ser His Ser Tyr Val Leu
 65 70 75 80
 Asn Lys Thr Arg Ala Ala Ala Val Val Gly Ile Asn Ser Glu Thr Ile
 85 90 95
 Met Lys Pro Ala Ser Ile Ser Glu Glu Glu Leu Leu Asn Leu Ile Asn
 100 105 110
 Lys Leu Asn Asn Asp Asp Asn Val Asp Gly Leu Leu Val Gln Leu Pro
 115 120 125
 Leu Pro Glu His Ile Asp Glu Arg Arg Ile Cys Asn Ala Val Ser Pro
 130 135 140
 Asp Lys Asp Val Asp Gly Phe His Val Ile Asn Val Gly Arg Met Cys
 145 150 155 160
 Leu Asp Gln Tyr Ser Met Leu Pro Ala Thr Pro Trp Gly Val Trp Glu
 165 170 175
 Ile Ile Lys Arg Thr Gly Ile Pro Thr Leu Gly Lys Asn Val Val Val
 180 185 190
 Ala Gly Arg Ser Lys Asn Val Gly Met Pro Ile Ala Met Leu Leu His
 195 200 205
 Thr Asp Gly Ala His Glu Arg Pro Gly Gly Asp Ala Thr Val Thr Ile
 210 215 220
 Ser His Arg Tyr Thr Pro Lys Glu Gln Leu Lys Lys His Thr Ile Leu
 225 230 235 240
 Ala Asp Ile Val Ile Ser Ala Ala Gly Ile Pro Asn Leu Ile Thr Ala
 245 250 255
 Asp Met Ile Lys Glu Gly Ala Ala Val Ile Asp Val Gly Ile Asn Arg
 260 265 270
 Val His Asp Pro Val Thr Ala Lys Pro Lys Leu Val Gly Asp Val Asp
 275 280 285
 Phe Glu Gly Val Arg Gln Lys Ala Gly Tyr Ile Thr Pro Val Pro Gly
 290 295 300

Gly Val Gly Pro Met Thr Val Ala Met Leu Met Lys Asn Thr Ile Ile
305 310 315 320

Ala Ala Lys Lys Val Leu Arg Leu Glu Glu Arg Glu Val Leu Lys Ser
325 330 335

Lys Glu Leu Gly Val Ala Thr Asn
340

<210> 57

<211> 1117

<212> DNA

<213> NM_006149 galectin 4, LGALS4

<220>

<221> CDS

<222> (57)..(1025)

<223>

<400> 57

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Met
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Ala Tyr Val Pro Ala Pro Gly Tyr Gln Pro Thr Tyr Asn Pro Thr Leu
5 10 15

cct tac tac cag ccc atc ccg ggc ggg etc aac gtg gga atg tct gtt 155
Pro Tyr Tyr Gln Pro Ile Pro Gly Gly Leu Asn Val Gly Met Ser Val
20 25 30

tac atc caa gga gtg gcc agc gag cac atg aag cgg ttc ttc gtg aac 203
Tyr Ile Gln Gly Val Ala Ser Glu His Met Lys Arg Phe Phe Val Asn
35 40 45

ttt gtg gtt ggg cag gat ccg ggc tca gac gtc gcc ttc cac ttc aat 251
Phe Val Val Gly Gln Asp Pro Gly Ser Asp Val Ala Phe His Phe Asn
50 55 60 65

ccg cgg ttt gac ggc tgg gac aag gtg gtc ttc aac acg ttg cag ggc 299
Pro Arg Phe Asp Gly Trp Asp Lys Val Val Phe Asn Thr Leu Gln Gly
70 75 80

ggg aag tgg ggc agc gag gag agg aag agg agc atg ccc ttc aaa aag 347
Gly Lys Trp Gly Ser Glu Glu Arg Lys Arg Ser Met Pro Phe Lys Lys
85 90 95

ggt gcc gcc ttt gag ctg gtc ttc ata gtc ctg gct gag cac tac aag 395
Gly Ala Ala Phe Glu Leu Val Phe Ile Val Leu Ala Glu His Tyr Lys
100 105 110

gtg gtg gta aat gga aat ccc ttc tat gag tac ggg cac cgg ctt ccc 443
Val Val Val Asn Gly Asn Pro Phe Tyr Glu Tyr Gly His Arg Leu Pro

144

115	120	125	
cta cag atg gtc acc cac ctg caa gtg gat ggg gat ctg caa ctt caa			491
Leu Gln Met Val Thr His Leu Gln Val Asp Gly Asp Leu Gln Leu Gln			
130	135	140	145
tca atc aac ttc atc gga ggc cag ccc ctc cgg ccc cag gga ccc ccg			539
Ser Ile Asn Phe Ile Gly Gly Gln Pro Leu Arg Pro Gln Gly Pro Pro			
150	155	160	
atg atg cca cct tac cct ggt ccc gga cat tgc cat caa cag ctg aac			587
Met Met Pro Pro Tyr Pro Gly Pro Gly His Cys His Gln Gln Leu Asn			
165	170	175	
agc ctg ccc acc atg gaa gga ccc cca acc ttc aac ccg cct gtg cca			635
Ser Leu Pro Thr Met Glu Gly Pro Pro Thr Phe Asn Pro Pro Val Pro			
180	185	190	
tat ttc ggg agg ctg caa gga ggg ctc aca gct cga aga acc atc atc			683
Tyr Phe Gly Arg Leu Gln Gly Gly Leu Thr Ala Arg Arg Thr Ile Ile			
195	200	205	
atc aag ggc tat gtg cct ccc aca ggc aag agc ttt gct atc aac ttc			731
Ile Lys Gly Tyr Val Pro Pro Thr Gly Lys Ser Phe Ala Ile Asn Phe			
210	215	220	225
aag gtg ggc tcc tca ggg gac ata gct ctg cac att aat ccc cgc atg			779
Lys Val Gly Ser Ser Gly Asp Ile Ala Leu His Ile Asn Pro Arg Met			
230	235	240	
ggc aac ggt acc gtg gtc cgg aac agc ctt ctg aat ggc tcg tgg gga			827
Gly Asn Gly Thr Val Val Arg Asn Ser Leu Leu Asn Gly Ser Trp Gly			
245	250	255	
tcc gag gag aag aag atc acc cac aac cca ttt ggt ccc gga cag ttc			875
Ser Glu Glu Lys Lys Ile Thr His Asn Pro Phe Gly Pro Gly Gln Phe			
260	265	270	
ttt gat ctg tcc att cgc tgt ggc ttg gat cgc ttc aag gtt tac gcc			923
Phe Asp Leu Ser Ile Arg Cys Gly Leu Asp Arg Phe Lys Val Tyr Ala			
275	280	285	
aat ggc cag cac ctc ttt gac ttt gcc cat cgc ctc tcg gcc ttc cag			971
Asn Gly Gln His Leu Phe Asp Phe Ala His Arg Leu Ser Ala Phe Gln			
290	295	300	305
agg gtg gac aca ttg gaa atc cag ggt gat gtc acc ttg tcc tat gtc			1019
Arg Val Asp Thr Leu Glu Ile Gln Gly Asp Val Thr Leu Ser Tyr Val			
310	315	320	
cag atc taatctattc ctggggccat aactcatggg aaaacagaat tatccctag			1075
Gln Ile			

gactcctttc taagccccta ataaaatgtc tgagggtgtc tc

1117

<210> 58

<211> 323

<212> PRT

<213> NM_006149 galectin 4, LGALS4

<400> 58

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 Leu Pro Tyr Tyr Gln Pro Ile Pro Gly Gly Leu Asn Val Gly Met Ser
 20 25 30
 Val Tyr Ile Gln Gly Val Ala Ser Glu His Met Lys Arg Phe Phe Val
 35 40 45
 Asn Phe Val Val Gly Gln Asp Pro Gly Ser Asp Val Ala Phe His Phe
 50 55 60
 Asn Pro Arg Phe Asp Gly Trp Asp Lys Val Val Phe Asn Thr Leu Gln
 65 70 75 80
 Gly Gly Lys Trp Gly Ser Glu Glu Arg Lys Arg Ser Met Pro Phe Lys
 85 90 95
 Lys Gly Ala Ala Phe Glu Leu Val Phe Ile Val Leu Ala Glu His Tyr
 100 105 110
 Lys Val Val Val Asn Gly Asn Pro Phe Tyr Glu Tyr Gly His Arg Leu
 115 120 125
 Pro Leu Gln Met Val Thr His Leu Gln Val Asp Gly Asp Leu Gln Leu
 130 135 140
 Gln Ser Ile Asn Phe Ile Gly Gly Gln Pro Leu Arg Pro Gln Gly Pro
 145 150 155 160
 Pro Met Met Pro Pro Tyr Pro Gly Pro Gly His Cys His Gln Gln Leu
 165 170 175
 Asn Ser Leu Pro Thr Met Glu Gly Pro Pro Thr Phe Asn Pro Pro Val
 180 185 190
 Pro Tyr Phe Gly Arg Leu Gln Gly Gly Leu Thr Ala Arg Arg Thr Ile
 195 200 205
 Ile Ile Lys Gly Tyr Val Pro Pro Thr Gly Lys Ser Phe Ala Ile Asn
 210 215 220
 Phe Lys Val Gly Ser Ser Gly Asp Ile Ala Leu His Ile Asn Pro Arg
 225 230 235 240
 Met Gly Asn Gly Thr Val Val Arg Asn Ser Leu Leu Asn Gly Ser Trp
 245 250 255
 Gly Ser Glu Glu Lys Lys Ile Thr His Asn Pro Phe Gly Pro Gly Gln
 260 265 270

Phe Phe Asp Leu Ser Ile Arg Cys Gly Leu Asp Arg Phe Lys Val Tyr
 275 280 285

Ala Asn Gly Gln His Leu Phe Asp Phe Ala His Arg Leu Ser Ala Phe
 290 295 300

Gln Arg Val Asp Thr Leu Glu Ile Gln Gly Asp Val Thr Leu Ser Tyr
 305 310 315 320

Val Gln Ile

<210> 59

<211> 3697

<212> DNA

<213> NM_004063 cadherin 17, CDH17

<220>

<221> CDS

<222> (121)..(2616)

<223>

<400> 59

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 gaaaaggact tttaaccacc attttgtgac ttacagaaag gaatttgaat aaagaaaact 120
 atg ata ctt cag gcc cat ctt cac tcc ctg tgt ctt ctt atg ctt tat 168
 Met Ile Leu Gln Ala His Leu His Ser Leu Cys Leu Leu Met Leu Tyr
 1 5 10 15
 ttg gca act gga tat ggc caa gag ggg aag ttt agt gga ccc ctg aaa 216
 Leu Ala Thr Gly Tyr Gly Gln Glu Gly Lys Phe Ser Gly Pro Leu Lys
 20 25 30
 ccc atg aca ttt tct att tat gaa ggc caa gaa ccg agt caa att ata 264
 Pro Met Thr Phe Ser Ile Tyr Glu Gly Gln Glu Pro Ser Gln Ile Ile
 35 40 45
 ttc cag ttt aag gcc aat cct cct gct gtg act ttt gaa cta act ggg 312
 Phe Gln Phe Lys Ala Asn Pro Pro Ala Val Thr Phe Glu Leu Thr Gly
 50 55 60
 gag aca gac aac ata ttt gtg ata gaa cgg gag gga ctt ctg tat tac 360
 Glu Thr Asp Asn Ile Phe Val Ile Glu Arg Gly Leu Leu Tyr Tyr
 65 70 75 80
 aac aga gcc ttg gac agg gaa aca aga tct act cac aat ctc cag gtt 408
 Asn Arg Ala Leu Asp Arg Glu Thr Arg Ser Thr His Asn Leu Gln Val
 85 90 95
 gca gcc ctg gac gct aat gga att ata gtg gag ggt cca gtc cct atc 456
 Ala Ala Leu Asp Ala Asn Gly Ile Ile Val Glu Gly Pro Val Pro Ile

100	105	110	
acc ata gaa gtg aag gac atc aac gac aat cga ccc acg ttt ctc cag			504
Thr Ile Glu Val Lys Asp Ile Asn Asp Asn Arg Pro Thr Phe Leu Gln			
115	120	125	
tca aag tac gaa ggc tca gta agg cag aac tct cgc cca gga aag ccc			552
Ser Lys Tyr Glu Gly Ser Val Arg Gln Asn Ser Arg Pro Gly Lys Pro			
130	135	140	
ttc ttg tat gtc aat gcc aca gac ctg gat gat ccg gcc act ccc aat			600
Phe Leu Tyr Val Asn Ala Thr Asp Leu Asp Asp Pro Ala Thr Pro Asn			
145	150	155	160
ggc cag ctt tat tac cag att gtc atc cag ctt ccc atg atc aac aat			648
Gly Gln Leu Tyr Tyr Gln Ile Val Ile Gln Leu Pro Met Ile Asn Asn			
165	170	175	
gtc atg tac ttt cag atc aac aac aaa acg gga gcc atc tct ctt acc			696
Val Met Tyr Phe Gln Ile Asn Asn Lys Thr Gly Ala Ile Ser Leu Thr			
180	185	190	
cga gag gga tct cag gaa ttg aat cct gct aag aat cct tcc tat aat			744
Arg Glu Gly Ser Gln Glu Leu Asn Pro Ala Lys Asn Pro Ser Tyr Asn			
195	200	205	
ctg gtg atc tca gtg aag gac atg gga ggc cag agt gag aat tcc ttc			792
Leu Val Ile Ser Val Lys Asp Met Gly Gly Gln Ser Glu Asn Ser Phe			
210	215	220	
agt gat acc aca tct gtg gat atc ata gtg aca gag aat att tgg aaa			840
Ser Asp Thr Thr Ser Val Asp Ile Ile Val Thr Glu Asn Ile Trp Lys			
225	230	235	240
gca cca aaa cct gtg gag atg gtg gaa aac tca act gat cct cac ccc			888
Ala Pro Lys Pro Val Glu Met Val Glu Asn Ser Thr Asp Pro His Pro			
245	250	255	
atc aaa atc act cag gtg cgg tgg aat gat ccc ggt gca caa tat tcc			936
Ile Lys Ile Thr Gln Val Arg Trp Asn Asp Pro Gly Ala Gln Tyr Ser			
260	265	270	
tta gtt gac aaa gag aag ctg cca aga ttc cca ttt tca att gac cag			984
Leu Val Asp Lys Glu Lys Leu Pro Arg Phe Pro Phe Ser Ile Asp Gln			
275	280	285	
gaa gga gat att tac gtg act cag ccc ttg gac cga gaa gaa aag gat			1032
Glu Gly Asp Ile Tyr Val Thr Gln Pro Leu Asp Arg Glu Glu Lys Asp			
290	295	300	
gca tat gtt ttt tat gca gtt gca aag gat gag tac gga aaa cca ctt			1080
Ala Tyr Val Phe Tyr Ala Val Ala Lys Asp Glu Tyr Gly Lys Pro Leu			
305	310	315	320
tca tat ccg ctg gaa att cat gta aaa gtt aaa gat att aat gat aat			1128
Ser Tyr Pro Leu Glu Ile His Val Lys Val Lys Asp Ile Asn Asp Asn			
325	330	335	
cca cct aca tgt ccg tca cca gta acc gta ttt gag gtc cag gag aat			1176
Pro Pro Thr Cys Pro Ser Pro Val Thr Val Phe Glu Val Gln Glu Asn			
340	345	350	
gaa cga ctg ggt aac agt atc ggg acc ctt act gca cat gac agg gat			1224
Glu Arg Leu Gly Asn Ser Ile Gly Thr Leu Thr Ala His Asp Arg Asp			
355	360	365	
gaa gaa aat act gcc aac agt ttt cta aac tac agg att gtg gag caa			1272
Glu Glu Asn Thr Ala Asn Ser Phe Leu Asn Tyr Arg Ile Val Glu Gln			

370	375	380	
act ccc aaa ctt ccc atg gat gga ctc ttc cta atc caa acc tat gct Thr Pro Lys Leu Pro Met Asp Gly Leu Phe Leu Ile Gln Thr Tyr Ala 385 390 395 400			1320
gga atg tta cag tta gct aaa cag tcc ttg aag aag caa gat act cct Gly Met Leu Gln Leu Ala Lys Gln Ser Leu Lys Lys Gln Asp Thr Pro 405 410 415			1368
cag tac aac tta acg ata gag gtg tct gac aaa gat ttc aag acc ctt Gln Tyr Asn Leu Thr Ile Glu Val Ser Asp Lys Asp Phe Lys Thr Leu 420 425 430			1416
tgt ttt gtg caa atc aac gtt att gat atc aat gat cag atc ccc atc Cys Phe Val Gln Ile Asn Val Ile Asp Ile Asn Asp Gln Ile Pro Ile 435 440 445			1464
ttt gaa aaa tca gat tat gga aac ctg act ctt gct gaa gac aca aac Phe Glu Lys Ser Asp Tyr Gly Asn Leu Thr Leu Ala Glu Asp Thr Asn 450 455 460			1512
att ggg tcc acc atc tta acc atc cag gcc act gat gct gat gag cca Ile Gly Ser Thr Ile Leu Thr Ile Gln Ala Thr Asp Ala Asp Glu Pro 465 470 475 480			1560
ttt act ggg agt tct aaa att ctg tat cat atc ata aag gga gac agt Phe Thr Gly Ser Ser Lys Ile Leu Tyr His Ile Ile Lys Gly Asp Ser 485 490 495			1608
gag gga cgc ctg ggg gtt gac aca gat ccc cat acc aac acc gga tat Glu Gly Arg Leu Gly Val Asp Thr Asp Pro His Thr Asn Thr Gly Tyr 500 505 510			1656
gtc ata att aaa aag cct ctt gat ttt gaa aca gca gct gtt tcc aac Val Ile Ile Lys Lys Pro Leu Asp Phe Glu Thr Ala Ala Val Ser Asn 515 520 525			1704
att gtg ttc aaa gca gaa aat cct gag cct cta gtg ttt ggt gtg aag Ile Val Phe Lys Ala Glu Asn Pro Glu Pro Leu Val Phe Gly Val Lys 530 535 540			1752
tac aat gca agt tct ttt gcc aag ttc acg ctt att gtg aca gat gtg Tyr Asn Ala Ser Ser Phe Ala Lys Phe Thr Leu Ile Val Thr Asp Val 545 550 555 560			1800
aat gaa gca cct caa ttt tcc caa cac gta ttc caa gcg aaa gtc agt Asn Glu Ala Pro Gln Phe Ser Gln His Val Phe Gln Ala Lys Val Ser 565 570 575			1848
gag gat gta gct ata ggc act aaa gtg ggc aat gtg act gcc aag gat Glu Asp Val Ala Ile Gly Thr Lys Val Gly Asn Val Thr Ala Lys Asp 580 585 590			1896
cca gaa ggt ctg gac ata agc tat tca ctg agg gga gac aca aga ggt Pro Glu Gly Leu Asp Ile Ser Tyr Ser Leu Arg Gly Asp Thr Arg Gly 595 600 605			1944
tgg ctt aaa att gac cac gtg act ggt gag atc ttt agt gtg gct cca Trp Leu Lys Ile Asp His Val Thr Gly Glu Ile Phe Ser Val Ala Pro 610 615 620			1992
ttg gac aga gaa gcc gga agt cca tat cgg gta caa gtg gtg gcc aca Leu Asp Arg Glu Ala Gly Ser Pro Tyr Arg Val Gln Val Val Ala Thr 625 630 635 640			2040
gaa gta ggg ggg tct tcc ttg agc tct gtg tca gag ttc cac ctg atc Glu Val Gly Gly Ser Ser Leu Ser Ser Val Ser Glu Phe His Leu Ile			2088

645	650	655	
ctt atg gat gtg aat gac aac cct ccc agg cta gcc aag gac tac acg			2136
Leu Met Asp Val Asn Asp Asn Pro Pro Arg Leu Ala Lys Asp Tyr Thr			
660	665	670	
ggc ttg ttc ttc tgc cat ccc ctc agt gca cct gga agt ctc att ttc			2184
Gly Leu Phe Phe Cys His Pro Leu Ser Ala Pro Gly Ser Leu Ile Phe			
675	680	685	
gag gct act gat gat gat cag cac tta ttt cgg ggt ccc cat ttt aca			2232
Glu Ala Thr Asp Asp Asp Gln His Leu Phe Arg Gly Pro His Phe Thr			
690	695	700	
ttt tcc ctc ggc agt gga agc tta caa aac gac tgg gaa gtt tcc aaa			2280
Phe Ser Leu Gly Ser Gly Ser Leu Gln Asn Asp Trp Glu Val Ser Lys			
705	710	715	720
atc aat ggt act cat gcc cga ctg tct acc agg cac aca gag ttt gag			2328
Ile Asn Gly Thr His Ala Arg Leu Ser Thr Arg His Thr Glu Phe Glu			
725	730	735	
gag agg gag tat gtc gtc ttg atc cgc atc aat gat ggg ggt cgg cca			2376
Glu Arg Glu Tyr Val Val Leu Ile Arg Ile Asn Asp Gly Gly Arg Pro			
740	745	750	
ccc ttg gaa ggc att gtt tct tta cca gtt aca ttc tgc agt tgt gtg			2424
Pro Leu Glu Gly Ile Val Ser Leu Pro Val Thr Phe Cys Ser Cys Val			
755	760	765	
gaa gga agt tgt ttc cgg cca gca ggt cac cag act ggg ata ccc act			2472
Glu Gly Ser Cys Phe Arg Pro Ala Gly His Gln Thr Gly Ile Pro Thr			
770	775	780	
gtg ggc atg gca gtt ggt ata ctg ctg acc acc ctt ctg gtg att ggt			2520
Val Gly Met Ala Val Gly Ile Leu Leu Thr Thr Leu Leu Val Ile Gly			
785	790	795	800
ata att tta gca gtt gtg ttt atc cgc ata aag aag gat aaa ggc aaa			2568
Ile Ile Leu Ala Val Val Phe Ile Arg Ile Lys Lys Asp Lys Gly Lys			
805	810	815	
gat aat gtt gaa agt gct caa gca tct gaa gtc aaa cct ctg aga agc			2616
Asp Asn Val Glu Ser Ala Gln Ala Ser Glu Val Lys Pro Leu Arg Ser			
820	825	830	
tgaatttgaa aaggaatggt tgaatttata tagcaagtgc tatttcagca acaaccatct			2676
catcctatta cttttcatct aacgtgcatt ataatttttt aaacagatat tccctcttgt			2736
cctttaatat ttgctaaata tttctttttt gaggtggagt cttgctctgt cgcccaggct			2796
ggagtacagt ggtgtgatcc cagctcactg caacctccgc ctcttggtt cacatgattc			2856
tcctgcctca gcttcctaag tagctgggtt tacaggcacc caccaccatg cccagctaata			2916
ttttgtatatt ttaatagaga cggggtttcg ccatttggcc aggtgtgtct tgaactcctg			2976
acgtcaagtg atctgcctgc cttggtctcc caatacaggc atgaaccact gcaccacct			3036
acttagatat ttcattgtgt atagacatta gagagatttt tcatttttcc atgacatttt			3096
tcctctctgc aaatggctta gctactgtg tttttccctt ttggggcaag acagactcat			3156
taaatattct gtacattttt tctttatcaa ggagatatat cagtgtgtgc tcatagaact			3216
gcctggattc catttatggt ttttctgatt ccactctgtg tcccttcat ccttgactcc			3276

tttggtat ttt cactgaattt caaacatttg tcagagaaga aaaacgtgag gactcaggaa 3336
 aaataaataa ataaaagaac agccttttcc cttagtatta acagaaatgt ttctgtgtca 3396
 ttaaccatct ttaatcaatg tgacatgttg ctctttggct gaaattcttc aacttgga 3456
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 ccagtcagct ggccagattt cctcactacc tgccatgcat acatgtgcg catgttttct 3576
 tcattcgtat gttagtaaag ttttggttat tatatatatta acatgtggaa gaaaacaaga 3636
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 a 3697

<210> 60

<211> 832

<212> PRT

<213> NM_004063 cadherin 17, CDH17

<400> 60

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Leu Ala Thr Gly Tyr Gly Gln Glu Gly Lys Phe Ser Gly Pro Leu Lys
20 25 30

Pro Met Thr Phe Ser Ile Tyr Glu Gly Gln Glu Pro Ser Gln Ile Ile
35 40 45

Phe Gln Phe Lys Ala Asn Pro Pro Ala Val Thr Phe Glu Leu Thr Gly
50 55 60

Glu Thr Asp Asn Ile Phe Val Ile Glu Arg Glu Gly Leu Leu Tyr Tyr
65 70 75 80

Asn Arg Ala Leu Asp Arg Glu Thr Arg Ser Thr His Asn Leu Gln Val
85 90 95

Ala Ala Leu Asp Ala Asn Gly Ile Ile Val Glu Gly Pro Val Pro Ile
100 105 110

Thr Ile Glu Val Lys Asp Ile Asn Asp Asn Arg Pro Thr Phe Leu Gln
115 120 125

Ser Lys Tyr Glu Gly Ser Val Arg Gln Asn Ser Arg Pro Gly Lys Pro
130 135 140

Phe Leu Tyr Val Asn Ala Thr Asp Leu Asp Asp Pro Ala Thr Pro Asn
145 150 155 160

Gly Gln Leu Tyr Tyr Gln Ile Val Ile Gln Leu Pro Met Ile Asn Asn
 165 170 175

Val Met Tyr Phe Gln Ile Asn Asn Lys Thr Gly Ala Ile Ser Leu Thr
 180 185 190

Arg Glu Gly Ser Gln Glu Leu Asn Pro Ala Lys Asn Pro Ser Tyr Asn
 195 200 205

Leu Val Ile Ser Val Lys Asp Met Gly Gly Gln Ser Glu Asn Ser Phe
 210 215 220

Ser Asp Thr Thr Ser Val Asp Ile Ile Val Thr Glu Asn Ile Trp Lys
 225 230 235 240

Ala Pro Lys Pro Val Glu Met Val Glu Asn Ser Thr Asp Pro His Pro
 245 250 255

Ile Lys Ile Thr Gln Val Arg Trp Asn Asp Pro Gly Ala Gln Tyr Ser
 260 265 270

Leu Val Asp Lys Glu Lys Leu Pro Arg Phe Pro Phe Ser Ile Asp Gln
 275 280 285

Glu Gly Asp Ile Tyr Val Thr Gln Pro Leu Asp Arg Glu Glu Lys Asp
 290 295 300

Ala Tyr Val Phe Tyr Ala Val Ala Lys Asp Glu Tyr Gly Lys Pro Leu
 305 310 315 320

Ser Tyr Pro Leu Glu Ile His Val Lys Val Lys Asp Ile Asn Asp Asn
 325 330 335

Pro Pro Thr Cys Pro Ser Pro Val Thr Val Phe Glu Val Gln Glu Asn
 340 345 350

Glu Arg Leu Gly Asn Ser Ile Gly Thr Leu Thr Ala His Asp Arg Asp
 355 360 365

Glu Glu Asn Thr Ala Asn Ser Phe Leu Asn Tyr Arg Ile Val Glu Gln
 370 375 380

Thr Pro Lys Leu Pro Met Asp Gly Leu Phe Leu Ile Gln Thr Tyr Ala
 385 390 395 400

Gly Met Leu Gln Leu Ala Lys Gln Ser Leu Lys Lys Gln Asp Thr Pro
 405 410 415

Gln Tyr Asn Leu Thr Ile Glu Val Ser Asp Lys Asp Phe Lys Thr Leu
 420 425 430

Cys Phe Val Gln Ile Asn Val Ile Asp Ile Asn Asp Gln Ile Pro Ile
 435 440 445
 Phe Glu Lys Ser Asp Tyr Gly Asn Leu Thr Leu Ala Glu Asp Thr Asn
 450 455 460
 Ile Gly Ser Thr Ile Leu Thr Ile Gln Ala Thr Asp Ala Asp Glu Pro
 465 470 475 480
 Phe Thr Gly Ser Ser Lys Ile Leu Tyr His Ile Ile Lys Gly Asp Ser
 485 490 495
 Glu Gly Arg Leu Gly Val Asp Thr Asp Pro His Thr Asn Thr Gly Tyr
 500 505 510
 Val Ile Ile Lys Lys Pro Leu Asp Phe Glu Thr Ala Ala Val Ser Asn
 515 520 525
 Ile Val Phe Lys Ala Glu Asn Pro Glu Pro Leu Val Phe Gly Val Lys
 530 535 540
 Tyr Asn Ala Ser Ser Phe Ala Lys Phe Thr Leu Ile Val Thr Asp Val
 545 550 555 560
 Asn Glu Ala Pro Gln Phe Ser Gln His Val Phe Gln Ala Lys Val Ser
 565 570 575
 Glu Asp Val Ala Ile Gly Thr Lys Val Gly Asn Val Thr Ala Lys Asp
 580 585 590
 Pro Glu Gly Leu Asp Ile Ser Tyr Ser Leu Arg Gly Asp Thr Arg Gly
 595 600 605
 Trp Leu Lys Ile Asp His Val Thr Gly Glu Ile Phe Ser Val Ala Pro
 610 615 620
 Leu Asp Arg Glu Ala Gly Ser Pro Tyr Arg Val Gln Val Val Ala Thr
 625 630 635 640
 Glu Val Gly Gly Ser Ser Leu Ser Ser Val Ser Glu Phe His Leu Ile
 645 650 655
 Leu Met Asp Val Asn Asp Asn Pro Pro Arg Leu Ala Lys Asp Tyr Thr
 660 665 670
 Gly Leu Phe Phe Cys His Pro Leu Ser Ala Pro Gly Ser Leu Ile Phe
 675 680 685
 Glu Ala Thr Asp Asp Asp Gln His Leu Phe Arg Gly Pro His Phe Thr
 690 695 700

Phe Ser Leu Gly Ser Gly Ser Leu Gln Asn Asp Trp Glu Val Ser Lys
705 710 715 720

Ile Asn Gly Thr His Ala Arg Leu Ser Thr Arg His Thr Glu Phe Glu
725 730 735

Glu Arg Glu Tyr Val Val Leu Ile Arg Ile Asn Asp Gly Gly Arg Pro
740 745 750

Pro Leu Glu Gly Ile Val Ser Leu Pro Val Thr Phe Cys Ser Cys Val
755 760 765

Glu Gly Ser Cys Phe Arg Pro Ala Gly His Gln Thr Gly Ile Pro Thr
770 775 780

Val Gly Met Ala Val Gly Ile Leu Leu Thr Thr Leu Leu Val Ile Gly
785 790 795 800

Ile Ile Leu Ala Val Val Phe Ile Arg Ile Lys Lys Asp Lys Gly Lys
805 810 815

Asp Asn Val Glu Ser Ala Gln Ala Ser Glu Val Lys Pro Leu Arg Ser
820 825 830

<210> 61

<211> 2920

<212> DNA

<213> NM_005588; meprin A, alpha

<220>

<221> CDS

<222> (10)..(2247)

<223>

<400> 61

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Met Ala Trp Ile Arg Ser Thr Cys Ile Leu Phe Thr Leu
1 5 10

ctt ttt gcc cac ata gca gct gta ccg att aag cat ctt cct gaa gaa 99
Leu Phe Ala His Ile Ala Val Pro Ile Lys His Leu Pro Glu Glu
15 20 25 30

aat gta cat gat gca gat ttt ggt gaa cag aag gat att tca gaa atc 147
Asn Val His Asp Ala Asp Phe Gly Glu Gln Lys Asp Ile Ser Glu Ile
35 40 45

aat tta gct gca gcc ttg gac ctc ttt caa ggg gac atc ctc ttg cag 195
Asn Leu Ala Ala Gly Leu Asp Leu Phe Gln Gly Asp Ile Leu Leu Gln

50	55	60	
aaa tcc aga aat ggc ctg aga gac cca aac acc agg tgg acg ttc ccc Lys Ser Arg Asn Gly Leu Arg Asp Pro Asn Thr Arg Trp Thr Phe Pro 65 70 75			243
att cct tac atc ttg gct gat aat ttg ggg ctg aat gct aaa gga gcc Ile Pro Tyr Ile Leu Ala Asp Asn Leu Gly Leu Asn Ala Lys Gly Ala 80 85 90			291
att ctg tat gcc ttt gag atg ttc cgt ctc aag tcc tgt gtg gat ttc Ile Leu Tyr Ala Phe Glu Met Phe Arg Leu Lys Ser Cys Val Asp Phe 95 100 105 110			339
aag ccc tat gaa gga gag agc tca tat atc ata ttt caa cag ttt gat Lys Pro Tyr Glu Gly Glu Ser Ser Tyr Ile Ile Phe Gln Gln Phe Asp 115 120 125			387
ggg tgc tgg tct gag gtt ggt gac caa cat gtg gga cag aac att tcc Gly Cys Trp Ser Glu Val Gly Asp Gln His Val Gly Gln Asn Ile Ser 130 135 140			435
att ggc caa gga tgt gcc tat aag gcc atc ata gaa cac gag atc ctg Ile Gly Gln Gly Cys Ala Tyr Lys Ala Ile Ile Glu His Glu Ile Leu 145 150 155			483
cat gct ttg gga ttt tac cac gag cag tca agg acg gac cgg gat gat His Ala Leu Gly Phe Tyr His Glu Gln Ser Arg Thr Asp Arg Asp Asp 160 165 170			531
tat gtg aac atc tgg tgg gac caa att ctt tca ggt tac cag cac aac Tyr Val Asn Ile Trp Trp Asp Gln Ile Leu Ser Gly Tyr Gln His Asn 175 180 185 190			579
ttt gac acc tat gat gat agc tta atc aca gac ctc aat aca ccc tat Phe Asp Thr Tyr Asp Asp Ser Leu Ile Thr Asp Leu Asn Thr Pro Tyr 195 200 205			627
gat tat gag tct ttg atg cac tac cag cct ttc tca ttt aac aag aat Asp Tyr Glu Ser Leu Met His Tyr Gln Pro Phe Ser Phe Asn Lys Asn 210 215 220			675
gca agt gtt ccc acc atc aca gcc aag atc cct gag ttt aac tcc att Ala Ser Val Pro Thr Ile Thr Ala Lys Ile Pro Glu Phe Asn Ser Ile 225 230 235			723
atc gga caa cgc ctg gat ttc agt gcc att gat tta gag agg ctg aac Ile Gly Gln Arg Leu Asp Phe Ser Ala Ile Asp Leu Glu Arg Leu Asn 240 245 250			771
cga atg tac aat tgc acc aca act cac act ctt ttg gac cac tgt act Arg Met Tyr Asn Cys Thr Thr Thr His Thr Leu Leu Asp His Cys Thr 255 260 265 270			819
ttt gag aag gca aac atc tgt gga atg att cag ggc acc aga gat gac Phe Glu Lys Ala Asn Ile Cys Gly Met Ile Gln Gly Thr Arg Asp Asp 275 280 285			867
act gac tgg gcc cat cag gac agt gct cag gct gga gaa gtg gat cac Thr Asp Trp Ala His Gln Asp Ser Ala Gln Ala Gly Glu Val Asp His 290 295 300			915
acc ttg ttg gga caa tgc aca ggt gcc ggc tac ttc atg cag ttc agc Thr Leu Leu Gly Gln Cys Thr Gly Ala Gly Tyr Phe Met Gln Phe Ser 305 310 315			963
acc agc tcg ggg tcc gcg gaa gag gca gcc cta ctg gag tct cgg att Thr Ser Ser Gly Ser Ala Glu Glu Ala Ala Leu Leu Glu Ser Arg Ile			1011

320	325	330	
ctt tac cca aag agg aag cag cag tgc ctg caa ttt ttc tat aaa atg Leu Tyr Pro Lys Arg Lys Gln Gln Cys Leu Gln Phe Phe Tyr Lys Met 335 340 345 350			1059
acg gga agt cct tca gac aga ctc gtt gtc tgg gtc agg agg gat gac Thr Gly Ser Pro Ser Asp Arg Leu Val Val Trp Val Arg Arg Asp Asp 355 360 365			1107
agc aca ggc aat gtt cgc aag ttg gtg aag gtg cag act ttt caa gga Ser Thr Gly Asn Val Arg Lys Leu Val Lys Val Gln Thr Phe Gln Gly 370 375 380			1155
gat gat gac cac aat tgg aaa att gcc cat gtg gtg ctc aaa gag gaa Asp Asp Asp His Asn Trp Lys Ile Ala His Val Val Leu Lys Glu Glu 385 390 395			1203
cag aag ttt cgc tac ctt ttc cag ggc aca aaa ggc gac cct cag aac Gln Lys Phe Arg Tyr Leu Phe Gln Gly Thr Lys Gly Asp Pro Gln Asn 400 405 410			1251
tca act ggg gga att tac cta gat gac atc act ctg aca gaa acc ccc Ser Thr Gly Gly Ile Tyr Leu Asp Asp Ile Thr Leu Thr Glu Thr Pro 415 420 425 430			1299
tgc ccc aca ggg gtc tgg aca gtc cgg aat ttc tcc caa gtc ctt gag Cys Pro Thr Gly Val Trp Thr Val Arg Asn Phe Ser Gln Val Leu Glu 435 440 445			1347
aac acc agc aaa ggg gac aag ctt cag agc cct cga ttc tac aat tcg Asn Thr Ser Lys Gly Asp Lys Leu Gln Ser Pro Arg Phe Tyr Asn Ser 450 455 460			1395
gag gga tat ggt ttt ggg gta act tta tac cca aat agc aga gaa agc Glu Gly Tyr Gly Phe Gly Val Thr Leu Tyr Pro Asn Ser Arg Glu Ser 465 470 475			1443
tct ggt tac ttg aga ctt gct ttt cat gtg tgc agt ggg gag aac gat Ser Gly Tyr Leu Arg Leu Ala Phe His Val Cys Ser Gly Glu Asn Asp 480 485 490			1491
gct atc ctg gag tgg ccg gta gaa aac aga cag gtg ata att acc atc Ala Ile Leu Glu Trp Pro Val Glu Asn Arg Gln Val Ile Ile Thr Ile 495 500 505 510			1539
ctt gac cag gag cct gat gtc cgg aac agg atg tcc tca agc atg gtg Leu Asp Gln Glu Pro Asp Val Arg Asn Arg Met Ser Ser Ser Met Val 515 520 525			1587
ttc act acc tcg aag tcg cac aca tct cca gcg ata aat gac act gtc Phe Thr Thr Ser Lys Ser His Thr Ser Pro Ala Ile Asn Asp Thr Val 530 535 540			1635
atc tgg gac agg ccg tcc agg gtg gga acc tat cat aca gac tgt aat Ile Trp Asp Arg Pro Ser Arg Val Gly Thr Tyr His Thr Asp Cys Asn 545 550 555			1683
tgt ttt aga agc atc gac ttg ggc tgg agt ggt ttc att tcc cac caa Cys Phe Arg Ser Ile Asp Leu Gly Trp Ser Gly Phe Ile Ser His Gln 560 565 570			1731
atg ctg aaa agg agg agt ttc ctg aaa aat gat gac ctc atc ata ttt Met Leu Lys Arg Arg Ser Phe Leu Lys Asn Asp Asp Leu Ile Ile Phe 575 580 585 590			1779
gtg gac ttt gaa gat atc acc cac ctc agc cag act gaa gtt ccc tct Val Asp Phe Glu Asp Ile Thr His Leu Ser Gln Thr Glu Val Pro Ser			1827

595	600	605	
aaa ggc aaa aga ctg agc ccc caa ggc ctc att ctc caa ggc cag gag			1875
Lys Gly Lys Arg Leu Ser Pro Gln Gly Leu Ile Leu Gln Gly Gln Glu			
610	615	620	
cag cag gtc tcc gaa gaa ggt tcg gga aag gcc atg tta gag gaa gcc			1923
Gln Gln Val Ser Glu Glu Gly Ser Gly Lys Ala Met Leu Glu Glu Ala			
625	630	635	
cta cct gtc agc ctg agc cag ggg cag ccc agc cga cag aag cgg tcg			1971
Leu Pro Val Ser Leu Ser Gln Gly Gln Pro Ser Arg Gln Lys Arg Ser			
640	645	650	
gtg gag aac aca ggc ccc ctg gag gac cat aac tgg cca cag tac ttc			2019
Val Glu Asn Thr Gly Pro Leu Glu Asp His Asn Trp Pro Gln Tyr Phe			
655	660	665	670
aga gac cca tgt gac cca aac cct tgc caa aat gac ggc atc tgt gtg			2067
Arg Asp Pro Cys Asp Pro Asn Pro Cys Gln Asn Asp Gly Ile Cys Val			
675	680	685	
aac gtg aag ggg atg gcg agc tgc agg tgc atc tct gga cat gct ttc			2115
Asn Val Lys Gly Met Ala Ser Cys Arg Cys Ile Ser Gly His Ala Phe			
690	695	700	
ttc tac acg ggg gag cgc tgt cag tcg gcc gag gtg cac ggc agt gtc			2163
Phe Tyr Thr Gly Glu Arg Cys Gln Ser Ala Glu Val His Gly Ser Val			
705	710	715	
ctg ggc atg gtg atc gga ggc acg gct ggc gtg atc ttc ttg acc ttc			2211
Leu Gly Met Val Ile Gly Gly Thr Ala Gly Val Ile Phe Leu Thr Phe			
720	725	730	
tcc atc atc gcc atc ctt tcc caa agg cca agg aag tgacctgcct			2257
Ser Ile Ile Ala Ile Leu Ser Gln Arg Pro Arg Lys			
735	740	745	
gctggcattg gccagaccac agcagcacct cctccatgca ggccttaact ttcccatgtt			2317
caatgcagtt tggggcagct tttttatcag ccttgctttg gataggacct ccaaggacta			2377
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aatcacttgt tttattgact gtctttccta tagactgtaa gctccatgag ggcaggcaca			2557
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aaa			2920

<210> 62

<211> 746

<212> PRT

<213> NM_005588; meprin A, alpha

<400> 62

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Ala His Ile Ala Ala Val Pro Ile Lys His Leu Pro Glu Glu Asn Val
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His Asp Ala Asp Phe Gly Glu Gln Lys Asp Ile Ser Glu Ile Asn Leu
 35 40 45

Ala Ala Gly Leu Asp Leu Phe Gln Gly Asp Ile Leu Leu Gln Lys Ser
 50 55 60

Arg Asn Gly Leu Arg Asp Pro Asn Thr Arg Trp Thr Phe Pro Ile Pro
 65 70 75 80

Tyr Ile Leu Ala Asp Asn Leu Gly Leu Asn Ala Lys Gly Ala Ile Leu
 85 90 95

Tyr Ala Phe Glu Met Phe Arg Leu Lys Ser Cys Val Asp Phe Lys Pro
 100 105 110

Tyr Glu Gly Glu Ser Ser Tyr Ile Ile Phe Gln Gln Phe Asp Gly Cys
 115 120 125

Trp Ser Glu Val Gly Asp Gln His Val Gly Gln Asn Ile Ser Ile Gly
 130 135 140

Gln Gly Cys Ala Tyr Lys Ala Ile Ile Glu His Glu Ile Leu His Ala
 145 150 155 160

Leu Gly Phe Tyr His Glu Gln Ser Arg Thr Asp Arg Asp Asp Tyr Val
 165 170 175

Asn Ile Trp Trp Asp Gln Ile Leu Ser Gly Tyr Gln His Asn Phe Asp
 180 185 190

Thr Tyr Asp Asp Ser Leu Ile Thr Asp Leu Asn Thr Pro Tyr Asp Tyr
 195 200 205

Glu Ser Leu Met His Tyr Gln Pro Phe Ser Phe Asn Lys Asn Ala Ser
 210 215 220

Val Pro Thr Ile Thr Ala Lys Ile Pro Glu Phe Asn Ser Ile Ile Gly
 225 230 235 240

Gln Arg Leu Asp Phe Ser Ala Ile Asp Leu Glu Arg Leu Asn Arg Met
245 250 255

Tyr Asn Cys Thr Thr Thr His Thr Leu Leu Asp His Cys Thr Phe Glu
260 265 270

Lys Ala Asn Ile Cys Gly Met Ile Gln Gly Thr Arg Asp Asp Thr Asp
275 280 285

Trp Ala His Gln Asp Ser Ala Gln Ala Gly Glu Val Asp His Thr Leu
290 295 300

Leu Gly Gln Cys Thr Gly Ala Gly Tyr Phe Met Gln Phe Ser Thr Ser
305 310 315 320

Ser Gly Ser Ala Glu Glu Ala Ala Leu Leu Glu Ser Arg Ile Leu Tyr
325 330 335

Pro Lys Arg Lys Gln Gln Cys Leu Gln Phe Phe Tyr Lys Met Thr Gly
340 345 350

Ser Pro Ser Asp Arg Leu Val Val Trp Val Arg Arg Asp Asp Ser Thr
355 360 365

Gly Asn Val Arg Lys Leu Val Lys Val Gln Thr Phe Gln Gly Asp Asp
370 375 380

Asp His Asn Trp Lys Ile Ala His Val Val Leu Lys Glu Glu Gln Lys
385 390 395 400

Phe Arg Tyr Leu Phe Gln Gly Thr Lys Gly Asp Pro Gln Asn Ser Thr
405 410 415

Gly Gly Ile Tyr Leu Asp Asp Ile Thr Leu Thr Glu Thr Pro Cys Pro
420 425 430

Thr Gly Val Trp Thr Val Arg Asn Phe Ser Gln Val Leu Glu Asn Thr
435 440 445

Ser Lys Gly Asp Lys Leu Gln Ser Pro Arg Phe Tyr Asn Ser Glu Gly
450 455 460

Tyr Gly Phe Gly Val Thr Leu Tyr Pro Asn Ser Arg Glu Ser Ser Gly
465 470 475 480

Tyr Leu Arg Leu Ala Phe His Val Cys Ser Gly Glu Asn Asp Ala Ile
485 490 495

Leu Glu Trp Pro Val Glu Asn Arg Gln Val Ile Ile Thr Ile Leu Asp
500 505 510

Gln Glu Pro Asp Val Arg Asn Arg Met Ser Ser Ser Met Val Phe Thr
515 520 525

Thr Ser Lys Ser His Thr Ser Pro Ala Ile Asn Asp Thr Val Ile Trp
530 535 540

Asp Arg Pro Ser Arg Val Gly Thr Tyr His Thr Asp Cys Asn Cys Phe
545 550 555 560

Arg Ser Ile Asp Leu Gly Trp Ser Gly Phe Ile Ser His Gln Met Leu
565 570 575

Lys Arg Arg Ser Phe Leu Lys Asn Asp Asp Leu Ile Ile Phe Val Asp
580 585 590

Phe Glu Asp Ile Thr His Leu Ser Gln Thr Glu Val Pro Ser Lys Gly
595 600 605

Lys Arg Leu Ser Pro Gln Gly Leu Ile Leu Gln Gly Gln Glu Gln Gln
610 615 620

Val Ser Glu Glu Gly Ser Gly Lys Ala Met Leu Glu Glu Ala Leu Pro
625 630 635 640

Val Ser Leu Ser Gln Gly Gln Pro Ser Arg Gln Lys Arg Ser Val Glu
645 650 655

Asn Thr Gly Pro Leu Glu Asp His Asn Trp Pro Gln Tyr Phe Arg Asp
660 665 670

Pro Cys Asp Pro Asn Pro Cys Gln Asn Asp Gly Ile Cys Val Asn Val
675 680 685

Lys Gly Met Ala Ser Cys Arg Cys Ile Ser Gly His Ala Phe Phe Tyr
690 695 700

Thr Gly Glu Arg Cys Gln Ser Ala Glu Val His Gly Ser Val Leu Gly
705 710 715 720

Met Val Ile Gly Gly Thr Ala Gly Val Ile Phe Leu Thr Phe Ser Ile
725 730 735

Ile Ala Ile Leu Ser Gln Arg Pro Arg Lys
740 745

<210> 63

<211> 8838

<212> DNA

<213> NM_015902 EDD, hyperplastic discs protein, DD5

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<221> CDS

<222> (34)..(8430)

<223>

<400> 63

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Val His Pro Leu Pro Gly Thr Glu Asp Gln Leu Asn Asp Arg Leu Arg	
10 15 20	
gaa gtt tct gag aag ctg aac aaa tat aat tta aac agc cac ccc cct	150
Glu Val Ser Glu Lys Leu Asn Lys Tyr Asn Leu Asn Ser His Pro Pro	
25 30 35	
ttg aat gta ttg gaa cag gct act att aaa cag tgt gtg gtg gga cca	198
Leu Asn Val Leu Glu Gln Ala Thr Ile Lys Gln Cys Val Val Gly Pro	
40 45 50 55	
aat cat gct gcc ttt ctt ctt gag gat ggt aga gtt tgc agg att ggt	246
Asn His Ala Ala Phe Leu Leu Glu Asp Gly Arg Val Cys Arg Ile Gly	
60 65 70	
ttt tca gta cag cca gac aga ttg gaa ttg ggt aaa cct gat aat aat	294
Phe Ser Val Gln Pro Asp Arg Leu Glu Leu Gly Lys Pro Asp Asn Asn	
75 80 85	
gat ggg tca aag ttg aac agc aac tcg ggg gca ggg agg acg tca agg	342
Asp Gly Ser Lys Leu Asn Ser Asn Ser Gly Ala Gly Arg Thr Ser Arg	
90 95 100	
cct ggt agg aca agc gac tct cca tgg ttt ctc tca ggt tct gag act	390
Pro Gly Arg Thr Ser Asp Ser Pro Trp Phe Leu Ser Gly Ser Glu Thr	
105 110 115	
cta ggc agg ctg gca ggc aac acc tta gga agc cgc tgg agt tct gga	438
Leu Gly Arg Leu Ala Gly Asn Thr Leu Gly Ser Arg Trp Ser Ser Gly	
120 125 130 135	
gtg ggt gga agt ggt gga gga tcc tct ggt agg tca tca gct gga gct	486
Val Gly Gly Ser Gly Gly Gly Ser Ser Gly Arg Ser Ser Ala Gly Ala	
140 145 150	
cga gat tcc cgc cgg cag act cga gtt att cgg aca gga cgg gat cga	534
Arg Asp Ser Arg Arg Gln Thr Arg Val Ile Arg Thr Gly Arg Asp Arg	
155 160 165	
ggg tct ggg ctt ttg ggc agt cag ccc cag cca gtt att cca gca tct	582
Gly Ser Gly Leu Leu Gly Ser Gln Pro Gln Pro Val Ile Pro Ala Ser	
170 175 180	
gtc att cca gag gag ctg att tca cag gcc caa gtt gtt tta caa ggc	630
Val Ile Pro Glu Glu Leu Ile Ser Gln Ala Gln Val Val Leu Gln Gly	
185 190 195	
aaa tcc aga agt gtc att att cga gaa ctt cag aga aca aat ctt gat	678
Lys Ser Arg Ser Val Ile Ile Arg Glu Leu Gln Arg Thr Asn Leu Asp	
200 205 210 215	

gtg aac ctt gct gta aat aat tta ctt agc cgg gat gat gaa gat gga Val Asn Leu Ala Val Asn Asn Leu Leu Ser Arg Asp Asp Glu Asp Gly 220 225 230	726
gat gat ggg gat gat aca gcc agc gaa tct tat ttg cct gga gag gat Asp Asp Gly Asp Asp Thr Ala Ser Glu Ser Tyr Leu Pro Gly Glu Asp 235 240 245	774
ctt atg tct ctc ctt gat gcc gac att cat tct gcc cac cca agt gtc Leu Met Ser Leu Leu Asp Ala Asp Ile His Ser Ala His Pro Ser Val 250 255 260	822
att att gat gca gat gcc atg ttt tct gaa gac att agc tat ttt ggt Ile Ile Asp Ala Asp Ala Met Phe Ser Glu Asp Ile Ser Tyr Phe Gly 265 270 275	870
tac cct tct ttt cgt cgt tca tca ctt tcc agg cta ggc tca tct cga Tyr Pro Ser Phe Arg Arg Ser Ser Leu Ser Arg Arg Leu Gly Ser Ser Arg 280 285 290 295	918
gtt ctc ctt ctt ccc tta gag aga gac tct gag ctg ttg cgt gaa cgt Val Leu Leu Leu Pro Leu Glu Arg Asp Ser Glu Leu Leu Arg Glu Arg 300 305 310	966
gaa tcc gtt tta cgt tta cgt gaa cga agg tgg ctt gat gga gcc tca Glu Ser Val Leu Arg Leu Arg Glu Arg Trp Leu Asp Gly Ala Ser 315 320 325	1014
ttt gat aat gaa agg ggt tct acc agc aag gaa gga gag cca aac ttg Phe Asp Asn Glu Arg Gly Ser Thr Ser Lys Glu Gly Glu Pro Asn Leu 330 335 340	1062
gat aag aag aat aca cct gtt caa agt cca gta tct cta gga gaa gat Asp Lys Lys Asn Thr Pro Val Gln Ser Pro Val Ser Leu Gly Glu Asp 345 350 355	1110
ttg cag tgg tgg cct gat aag gat gga aca aaa ttc atc tgt att ggg Leu Gln Trp Trp Pro Asp Lys Asp Gly Thr Lys Phe Ile Cys Ile Gly 360 365 370 375	1158
gct ctg tat tct gaa ctt ctg gct gtc agc agt aaa gga gaa ctt tat Ala Leu Tyr Ser Glu Leu Leu Ala Val Ser Ser Lys Gly Glu Leu Tyr 380 385 390	1206
cag tgg aaa tgg agt gaa tct gag cct tac aga aat gcc cag aat cct Gln Trp Lys Trp Ser Glu Ser Glu Pro Tyr Arg Asn Ala Gln Asn Pro 395 400 405	1254
tca tta cat cat cca cga gca aca ttt ttg ggg tta acc aat gaa aag Ser Leu His His Pro Arg Ala Thr Phe Leu Gly Leu Thr Asn Glu Lys 410 415 420	1302
ata gtc ctc ctg tct gca aat agc ata aga gca act gta gct aca gaa Ile Val Leu Leu Ser Ala Asn Ser Ile Arg Ala Thr Val Ala Thr Glu 425 430 435	1350
aat aac aag gtt gct aca tgg gtg gat gaa act tta agt tct gtg gct Asn Asn Lys Val Ala Thr Trp Val Asp Glu Thr Leu Ser Ser Val Ala 440 445 450 455	1398
tct aaa tta gag cac act gct cag act tac tct gaa ctt caa gga gag Ser Lys Leu Glu His Thr Ala Gln Thr Tyr Ser Glu Leu Gln Gly Glu 460 465 470	1446
cgg ata gtt tct tta cat tgc tgt gcc ctt tac acc tgc gct cag ctg Arg Ile Val Ser Leu His Cys Cys Ala Leu Tyr Thr Cys Ala Gln Leu 475 480 485	1494

gaa aac agt tta tat tgg tgg ggt gta gtt cct ttt agt caa agg aag Glu Asn Ser Leu Tyr Trp Trp Gly Val Val Pro Phe Ser Gln Arg Lys 490 495 500	1542
aaa atg tta gag aaa gct aga gca aaa aat aaa aag cct aaa tcc agt Lys Met Leu Glu Lys Ala Arg Ala Lys Asn Lys Lys Pro Lys Ser Ser 505 510 515	1590
gct ggt att tct tca atg ccg aac atc act gtt ggt acc cag gta tgc Ala Gly Ile Ser Ser Met Pro Asn Ile Thr Val Gly Thr Gln Val Cys 520 525 530 535	1638
ttg aga aat aat cct ctt tat cat gct gga gca gtt gca ttt tca att Leu Arg Asn Asn Pro Leu Tyr His Ala Gly Ala Val Ala Phe Ser Ile 540 545 550	1686
agt gct ggg att cct aaa gtt ggt gtc tta atg gag tca gtt tgg aat Ser Ala Gly Ile Pro Lys Val Gly Val Leu Met Glu Ser Val Trp Asn 555 560 565	1734
atg aat gac agc tgt aga ttt caa ctt aga tct cct gaa agc ttg aaa Met Asn Asp Ser Cys Arg Phe Gln Leu Arg Ser Pro Glu Ser Leu Lys 570 575 580	1782
aac atg gaa aaa gct agc aaa act act gaa gct aag cct gaa agt aag Asn Met Glu Lys Ala Ser Lys Thr Thr Glu Ala Lys Pro Glu Ser Lys 585 590 595	1830
cag gag cca gtg aaa aca gaa atg ggt cct cca cca tct cca gca tcc Gln Glu Pro Val Lys Thr Glu Met Gly Pro Pro Ser Pro Ala Ser 600 605 610 615	1878
acg tgt agt gat gca tcc tca att gcc agc agt gca tca atg cca tac Thr Cys Ser Asp Ala Ser Ser Ile Ala Ser Ser Ala Ser Met Pro Tyr 620 625 630	1926
aaa cga cga cgg tca acc cct gca cca aaa gaa gag gaa aag gtg aat Lys Arg Arg Arg Ser Thr Pro Ala Pro Lys Glu Glu Glu Lys Val Asn 635 640 645	1974
gaa gag cag tgg tct ctt cgg gaa gtg gtt ttt gtg gaa gat gtc aag Glu Glu Gln Trp Ser Leu Arg Glu Val Val Phe Val Glu Asp Val Lys 650 655 660	2022
aat gtt cct gtt ggc aag gtg cta aaa gta gat ggt gcc tat gtt gct Asn Val Pro Val Gly Lys Val Leu Lys Val Asp Gly Ala Tyr Val Ala 665 670 675	2070
gta aaa ttt cca gga acc tcc agt aat act aac tgt cag aac agc tct Val Lys Phe Pro Gly Thr Ser Ser Asn Thr Asn Cys Gln Asn Ser Ser 680 685 690 695	2118
ggt cca gat gct gac cct tct tct ctc ctg cag gat tgt agg tta ctt Gly Pro Asp Ala Asp Pro Ser Ser Leu Leu Gln Asp Cys Arg Leu Leu 700 705 710	2166
aga att gat gaa ttg cag gtt gtc aaa act ggt gga aca ccg aag gtt Arg Ile Asp Glu Leu Gln Val Val Lys Thr Gly Gly Thr Pro Lys Val 715 720 725	2214
ccc gac tgt ttc caa agg act cct aaa aag ctt tgt ata cct gaa aaa Pro Asp Cys Phe Gln Arg Thr Pro Lys Lys Leu Cys Ile Pro Glu Lys 730 735 740	2262
aca gaa ata tta gca gtg aat gta gat tcc aaa ggt gtt cat gct gtt Thr Glu Ile Leu Ala Val Asn Val Asp Ser Lys Gly Val His Ala Val 745 750 755	2310

ctg aag act gga aat tgg gtg cga tac tgt atc ttt gat ctt gct aca Leu Lys Thr Gly Asn Trp Val Arg Tyr Cys Ile Phe Asp Leu Ala Thr 760 765 770 775	2358
gga aaa gca gaa cag gaa aat aat ttt cct aca agc agc att gct ttc Gly Lys Ala Glu Gln Glu Asn Asn Phe Pro Thr Ser Ser Ile Ala Phe 780 785 790	2406
ctt ggt cag aat gag agg aat gta gcc att ttc act gct gga cag gaa Leu Gly Gln Asn Glu Arg Asn Val Ala Ile Phe Thr Ala Gly Gln Glu 795 800 805	2454
tct ccc att att ctt cga gat gga aat ggt acc atc tac cca atg gcc Ser Pro Ile Ile Leu Arg Asp Gly Asn Gly Thr Ile Tyr Pro Met Ala 810 815 820	2502
aaa gat tgc atg gga gga ata agg gat ccc gat tgg ctg gat ctt cca Lys Asp Cys Met Gly Gly Ile Arg Asp Pro Asp Trp Leu Asp Leu Pro 825 830 835	2550
cct att agt agt ctt gga atg ggt gtg cat tct tta ata aat ctt cct Pro Ile Ser Ser Leu Gly Met Gly Val His Ser Leu Ile Asn Leu Pro 840 845 850 855	2598
gcc aat tca aca atc aaa aag aaa gct gct gtt atc atc atg gct gta Ala Asn Ser Thr Ile Lys Lys Lys Ala Val Ile Ile Met Ala Val 860 865 870	2646
gag aaa caa acc tta atg caa cac att ctg cgc tgt gac tat gag gcc Glu Lys Gln Thr Leu Met Gln His Ile Leu Arg Cys Asp Tyr Glu Ala 875 880 885	2694
tgt cga caa tat cta atg aat ctt gag caa gcg gtt gtt tta gag cag Cys Arg Gln Tyr Leu Met Asn Leu Glu Gln Ala Val Val Leu Glu Gln 890 895 900	2742
aat cta cag atg ctg cag aca ttc atc agc cac aga tgt gat gga aat Asn Leu Gln Met Leu Gln Thr Phe Ile Ser His Arg Cys Asp Gly Asn 905 910 915	2790
cga aat att ttg cat gct tgt gta tca gtt tgc ttt cca acc agc aat Arg Asn Ile Leu His Ala Cys Val Ser Val Cys Phe Pro Thr Ser Asn 920 925 930 935	2838
aaa gaa act aaa gaa gaa gag gaa gcg gag cgt tct gaa aga aat aca Lys Glu Thr Lys Glu Glu Glu Glu Ala Glu Arg Ser Glu Arg Asn Thr 940 945 950	2886
ttt gca gaa agg ctt tct gct gtt gag gcc att gca aat gca ata tca Phe Ala Glu Arg Leu Ser Ala Val Glu Ala Ile Ala Asn Ala Ile Ser 955 960 965	2934
gtt gtt tca agt aat ggc cca ggt aat cgg gct gga tca tca agt agc Val Val Ser Ser Asn Gly Pro Gly Asn Arg Ala Gly Ser Ser Ser Ser 970 975 980	2982
cga agt ttg aga tta cgg gaa atg atg aga cgt tcg ttg aga gca gct Arg Ser Leu Arg Leu Arg Glu Met Met Arg Arg Ser Leu Arg Ala Ala 985 990 995	3030
ggt ttg ggt aga cat gaa gct gga gct tca tcc agt gac cac cag Gly Leu Gly Arg His Glu Ala Gly Ala Ser Ser Ser Asp His Gln 1000 1005 1010	3075
gat cca gtt tca ccc ccc ata gct ccc cct agt tgg gtt cct gac Asp Pro Val Ser Pro Pro Ile Ala Pro Pro Ser Trp Val Pro Asp 1015 1020 1025	3120

cct Pro 1030	cct gcg atg gat Pro Ala Met Asp 1035	cct Pro 1035	gat ggt gac att gat Asp Gly Asp Ile 1040	ttt atc ctg gcc Phe Ile Leu Ala	3165
ccc Pro 1045	gct gtg gga tct ctt Ala Val Gly Ser 1050	acc aca gca gca acc Thr Thr Ala Ala Thr 1055	ggt act ggt caa Gly Thr Gly Gln	3210	
gga Gly 1060	cca agc acc tcc act Pro Ser Thr Ser 1065	att cca ggt cct tcc Ile Pro Gly Pro Ser 1070	aca gag cca tct Thr Glu Pro Ser	3255	
gta Val 1075	gta gaa tcc aag gat Val Glu Ser Lys Asp 1080	cga aag gcg aat gct Arg Lys Ala Asn Ala 1085	cat ttt ata ttg His Phe Ile Leu	3300	
aaa Lys 1090	ttg tta tgt gac agt Leu Leu Cys Asp Ser 1095	gtg gtt ctc cag ccc Val Val Leu Gln Pro 1100	tat cta cga gaa Tyr Leu Arg Glu	3345	
ctt Leu 1105	ctt tct gcc aag gat Leu Ser Ala Lys Asp 1110	gca aga ggg atg acc Ala Arg Gly Met Thr 1115	cca ttt atg tca Pro Phe Met Ser	3390	
gct Ala 1120	gta agt ggc cga gct Val Ser Gly Arg Ala 1125	tat cct gct gca att Tyr Pro Ala Ala Ile 1130	acc atc tta gaa Thr Ile Leu Glu	3435	
act Thr 1135	gct cag aaa att gca Ala Gln Lys Ile Ala 1140	aaa gct gaa ata tcc Lys Ala Glu Ile Ser 1145	tca agt gaa aaa Ser Ser Glu Lys	3480	
gag Glu 1150	gaa gat gta ttc atg Glu Asp Val Phe Met 1155	gga atg gtt tgc cca Gly Met Val Cys Pro 1160	tca ggt acc aac Ser Gly Thr Asn	3525	
cct Pro 1165	gat gac tct cct tta Asp Asp Ser Pro Leu 1170	tat gtt tta tgt tgt Tyr Val Leu Cys Cys 1175	aat gac act tgc Asn Asp Thr Cys	3570	
agt Ser 1180	ttt aca tgg act gga Phe Thr Trp Thr Gly 1185	gca gag cac att aac Ala Glu His Ile Asn 1190	cag gat att ttt Gln Asp Ile Phe	3615	
gag Glu 1195	tgt cga act tgt ggc Cys Arg Thr Cys Gly 1200	ttg ctg gag tca ctg Leu Leu Glu Ser Leu 1205	tgt tgt tgt acg Cys Cys Cys Thr	3660	
gaa Glu 1210	tgt gca agg gtt tgt Cys Ala Arg Val Cys 1215	cat aaa ggt cat gat His Lys Gly His Asp 1220	tgc aaa ctc aaa Cys Lys Leu Lys	3705	
cgg Arg 1225	aca tca cca aca gcc Thr Ser Pro Thr Ala 1230	tac tgt gat tgt tgg Tyr Cys Asp Cys Trp 1235	gag aaa tgt aaa Glu Lys Cys Lys	3750	
tgt Cys 1240	aaa act ctt att gct Lys Thr Leu Ile Ala 1245	gga cag aaa tct gct Gly Gln Lys Ser Ala 1250	cgt ctt gat cta Arg Leu Asp Leu	3795	
ctt Leu 1255	tat cgc ctg ctc act Tyr Arg Leu Leu Thr 1260	gct act aat ctg gtt Ala Thr Asn Leu Val 1265	act ctg cca aac Thr Leu Pro Asn	3840	
agc Ser 1270	agg gga gag cac ctc Arg Gly Glu His Leu 1275	tta cta ttc tta gta Leu Leu Phe Leu Val 1280	cag aca gtc gca Gln Thr Val Ala	3885	

agg Arg 1285	cag Gln Thr	acg Val	gtg Glu	gag His	cat 1290	tgt Cys	caa Gln	tac Tyr	agg Arg	cca Pro	cct Pro	cga Arg	atc Ile	agg Arg	3930
gaa Glu 1300	gat Asp	cgt Arg	aac Asn	cga Arg	aaa Lys 1305	aca Thr	gcc Ala	agt Ser	cct Pro	gaa Glu 1310	gat Asp	tca Ser	gat Asp	atg Met	3975
cca Pro 1315	gat Asp	cat His	gat Asp	tta Leu	gag Glu 1320	cct Pro	cca Pro	aga Arg	ttt Phe	gcc Ala 1325	cag Gln	ctt Leu	gca Ala	ttg Leu	4020
gag Glu 1330	cgt Arg	gtt Val	cta Leu	cag Gln	gac Asp 1335	tgg Trp	aat Asn	gcc Ala	ttg Leu	aaa Lys 1340	tct Ser	atg Met	att Ile	atg Met	4065
ttt Phe 1345	ggg Gly	tcg Ser	cag Gln	gag Glu	aat Asn 1350	aaa Lys	gac Asp	cct Pro	ctt Leu	agt Ser 1355	gcc Ala	agc Ser	agt Ser	aga Arg	4110
ata Ile 1360	ggc Gly	cat His	ctt Leu	ttg Leu	cca Pro 1365	gaa Glu	gag Glu	caa Gln	gta Val	tac Tyr 1370	ctc Leu	aat Asn	cag Gln	caa Gln	4155
agt Ser 1375	ggc Gly	aca Thr	att Ile	cg Arg	ctg Leu 1380	gac Asp	tgt Cys	ttc Phe	act Thr	cat His 1385	tgc Cys	ctt Leu	ata Ile	gtt Val	4200
aag Lys 1390	tgt Cys	aca Thr	gca Ala	gat Asp	att Ile 1395	ttg Leu	ctt Leu	tta Leu	gat Asp	act Thr 1400	cta Leu	cta Leu	ggt Gly	aca Thr	4245
cta Leu 1405	gtg Val	aaa Lys	gaa Glu	ctc Leu	caa Gln 1410	aac Asn	aaa Lys	tat Tyr	aca Thr	cct Pro 1415	gga Gly	cgt Arg	aga Arg	gaa Glu	4290
gaa Glu 1420	gct Ala	att Ile	gct Ala	gtg Val	aca Thr 1425	atg Met	agg Arg	ttt Phe	cta Leu	cgt Arg 1430	tca Ser	gtg Val	gca Ala	aga Arg	4335
gtt Val 1435	ttt Phe	gtt Val	att Ile	ctg Leu	agt Ser 1440	gtg Val	gaa Glu	atg Met	gct Ala	tca Ser 1445	tcc Ser	aaa Lys	aag Lys	aaa Lys	4380
aac Asn 1450	aac Asn	ttt Phe	att Ile	cca Pro	cag Gln 1455	cca Pro	att Ile	gga Gly	aaa Lys	tgc Cys 1460	aag Lys	cgt Arg	gta Val	ttc Phe	4425
caa Gln 1465	gca Ala	ttg Leu	cta Leu	cct Pro	tac Tyr 1470	gct Ala	gtg Val	gaa Glu	gaa Glu	ttg Leu 1475	tgc Cys	aac Asn	gta Val	gca Ala	4470
gag Glu 1480	tca Ser	ctg Leu	att Ile	gtt Val	cct Pro 1485	gtc Val	aga Arg	atg Met	ggg Gly	att Ile 1490	gct Ala	cgt Arg	cca Pro	act Thr	4515
gca Ala 1495	cca Pro	ttt Phe	acc Thr	ctg Leu	gct Ala 1500	agt Ser	act Thr	agc Ser	ata Ile	gat Asp 1505	gcc Ala	atg Met	cag Gln	ggc Gly	4560
agt Ser 1510	gaa Glu	gaa Glu	tta Leu	ttt Phe	tca Ser 1515	gtg Val	gaa Glu	cca Pro	cta Leu	cca Pro 1520	cca Pro	cga Arg	cca Pro	tca Ser	4605
tct Ser 1525	gat Asp	cag Gln	tct Ser	agc Ser	agc Ser 1530	tcc Ser	agt Ser	cag Gln	tct Ser	cag Gln 1535	tca Ser	tcc Ser	tac Tyr	atc Ile	4650

atc Ile 1540	agg aat cca cag cag Arg Asn Pro Gln Gln 1545	agg cgc atc agc cag Arg Arg Ile Ser Gln 1550	tca cag ccc gtt Ser Gln Pro Val	4695
cgg Arg 1555	ggc aga gat gaa gaa Gly Arg Asp Glu Glu 1560	cag gat gat att gtt Gln Asp Asp Ile Val 1565	tca gca gat gtg Ser Ala Asp Val	4740
gaa Glu 1570	gag gtt gag gtg gtg Glu Val Glu Val Val 1575	gag ggt gtg gct gga Glu Gly Val Ala Gly 1580	gaa gag gat cat Glu Glu Asp His	4785
cat His 1585	gat gaa cag gaa gaa Asp Glu Gln Glu Glu 1590	cac ggg gaa gaa aat His Gly Glu Glu Asn 1595	gct gag gca gag Ala Glu Ala Glu	4830
gga Gly 1600	caa cat gat gag cat Gln His Asp Glu His 1605	gat gaa gac ggg agt Asp Glu Asp Gly Ser 1610	gat atg gag ctg Asp Met Glu Leu	4875
gac Asp 1615	ttg tta gca gca gct Leu Leu Ala Ala Ala 1620	gaa aca gaa agt gat Glu Thr Glu Ser Asp 1625	agt gaa agt aac Ser Glu Ser Asn	4920
cac His 1630	agc aac caa gat aat Ser Asn Gln Asp Asn 1635	gct agt ggg cgc aga Ala Ser Gly Arg Arg 1640	agc gtt gtc act Ser Val Val Thr	4965
gca Ala 1645	gca act gct ggt tca Ala Thr Ala Gly Ser 1650	gaa gca gga gca agc Glu Ala Gly Ala Ser 1655	agt gtt cct gcc Ser Val Pro Ala	5010
ttc Phe 1660	ttt tct gaa gat gat Phe Ser Glu Asp Asp 1665	tct caa tcg aat gac Ser Gln Ser Asn Asp 1670	tca agt gat tct Ser Ser Asp Ser	5055
gat Asp 1675	agc agt agt agt cag Ser Ser Ser Ser Gln 1680	agt gac gac ata gaa Ser Asp Asp Ile Glu 1685	cag gag acc ttt Gln Glu Thr Phe	5100
atg Met 1690	ctt gat gag cca tta Leu Asp Glu Pro Leu 1695	gaa aga acc aca aat Glu Arg Thr Thr Asn 1700	agc tcc cat gcc Ser Ser His Ala	5145
aat Asn 1705	ggt gct gcc caa gct Gly Ala Ala Gln Ala 1710	ccc cgt tca atg cag Pro Arg Ser Met Gln 1715	tgg gct gtc cgc Trp Ala Val Arg	5190
aac Asn 1720	acc cag cat cag cga Thr Gln His Gln Arg 1725	gca gcc agt aca gcc Ala Ala Ser Thr Ala 1730	cct tcc agt aca Pro Ser Ser Thr	5235
tct Ser 1735	aca cca gca gca agt Thr Pro Ala Ala Ser 1740	tca gcg ggt ttg att Ser Ala Gly Leu Ile 1745	tat att gat cct Tyr Ile Asp Pro	5280
tca Ser 1750	aac tta cgc cgg agt Asn Leu Arg Arg Ser 1755	ggt acc atc agt aca Gly Thr Ile Ser Thr 1760	agt gct gca gct Ser Ala Ala Ala	5325
gca Ala 1765	gca gct gct ttg gaa Ala Ala Ala Leu Glu 1770	gct agc aac gcc agc Ala Ser Asn Ala Ser 1775	agt tac cta aca Ser Tyr Leu Thr	5370
tct Ser 1780	gca agc agt tta gcc Ala Ser Ser Ser Leu Ala 1785	agg gct tac agc att Arg Ala Tyr Ser Ile 1790	gtc att aga caa Val Ile Arg Gln	5415

atc	tcg	gac	ttg	atg	ggc	ctt	att	cct	aag	tat	aat	cac	cta	gta	5460
Ile	Ser	Asp	Leu	Met	Gly	Leu	Ile	Pro	Lys	Tyr	Asn	His	Leu	Val	
1795					1800					1805					
tac	tct	cag	att	cca	gca	gct	gtg	aaa	ttg	act	tac	caa	gat	gca	5505
Tyr	Ser	Gln	Ile	Pro	Ala	Ala	Val	Lys	Leu	Thr	Tyr	Gln	Asp	Ala	
1810					1815					1820					
gta	aac	tta	cag	aac	tat	gta	gaa	gaa	aag	ctt	att	ccc	act	tgg	5550
Val	Asn	Leu	Gln	Asn	Tyr	Val	Glu	Glu	Lys	Leu	Ile	Pro	Thr	Trp	
1825					1830					1835					
aac	tgg	atg	gtc	agt	att	atg	gat	tct	act	gaa	gct	caa	tta	cgt	5595
Asn	Trp	Met	Val	Ser	Ile	Met	Asp	Ser	Thr	Glu	Ala	Gln	Leu	Arg	
1840					1845					1850					
tat	ggt	tct	gca	tta	gca	tct	gct	ggt	gat	cct	gga	cat	cca	aat	5640
Tyr	Gly	Ser	Ala	Leu	Ala	Ser	Ala	Gly	Asp	Pro	Gly	His	Pro	Asn	
1855					1860					1865					
cat	cct	ctt	cac	gct	tct	cag	aat	tca	gcg	aga	aga	gag	agg	atg	5685
His	Pro	Leu	His	Ala	Ser	Gln	Asn	Ser	Ala	Arg	Arg	Glu	Arg	Met	
1870					1875					1880					
act	gcg	cga	gaa	gaa	gct	agc	tta	cga	aca	ctt	gaa	ggc	aga	cga	5730
Thr	Ala	Arg	Glu	Glu	Ala	Ser	Leu	Arg	Thr	Leu	Glu	Gly	Arg	Arg	
1885					1890					1895					
cgt	gcc	acc	ttg	ctt	agc	gcc	cgt	caa	gga	atg	atg	tct	gca	cga	5775
Arg	Ala	Thr	Leu	Leu	Ser	Ala	Arg	Gln	Gly	Met	Met	Ser	Ala	Arg	
1900					1905					1910					
gga	gac	ttc	cta	aat	tat	gct	ctg	tct	cta	atg	cgg	tct	cat	aat	5820
Gly	Asp	Phe	Leu	Asn	Tyr	Ala	Leu	Ser	Leu	Met	Arg	Ser	His	Asn	
1915					1920					1925					
gat	gag	cat	tct	gat	gtt	ctt	cca	gtt	ttg	gat	gtt	tgc	tca	ttg	5865
Asp	Glu	His	Ser	Asp	Val	Leu	Pro	Val	Leu	Asp	Val	Cys	Ser	Leu	
1930					1935					1940					
aag	cat	gtg	gca	tat	gtt	ttt	caa	gca	ctt	ata	tac	tgg	att	aag	5910
Lys	His	Val	Ala	Tyr	Val	Phe	Gln	Ala	Leu	Ile	Tyr	Trp	Ile	Lys	
1945					1950					1955					
gca	atg	aat	cag	cag	aca	aca	ttg	gat	aca	cct	caa	cta	gaa	cgc	5955
Ala	Met	Asn	Gln	Gln	Thr	Thr	Leu	Asp	Thr	Pro	Gln	Leu	Glu	Arg	
1960					1965					1970					
aaa	agg	acg	cga	gaa	ctc	ttg	gaa	ctg	ggt	att	gat	aat	gaa	gat	6000
Lys	Arg	Thr	Arg	Glu	Leu	Leu	Glu	Leu	Gly	Ile	Asp	Asn	Glu	Asp	
1975					1980					1985					
tca	gaa	cat	gaa	aat	gat	gat	gac	acc	aat	caa	agt	gct	act	ttg	6045
Ser	Glu	His	Glu	Asn	Asp	Asp	Asp	Thr	Asn	Gln	Ser	Ala	Thr	Leu	
1990					1995					2000					
aat	gat	aag	gat	gat	gac	tct	ctt	cct	gca	gaa	act	ggc	caa	aac	6090
Asn	Asp	Lys	Asp	Asp	Asp	Ser	Leu	Pro	Ala	Glu	Thr	Gly	Gln	Asn	
2005					2010					2015					
cat	cca	ttt	ttc	cga	cgt	tca	gac	tcc	atg	aca	ttc	ctt	ggg	tgt	6135
His	Pro	Phe	Phe	Arg	Arg	Ser	Asp	Ser	Met	Thr	Phe	Leu	Gly	Cys	
2020					2025					2030					
ata	ccc	cca	aat	cca	ttt	gaa	gtg	cct	ctg	gct	gaa	gcc	atc	ccc	6180
Ile	Pro	Pro	Asn	Pro	Phe	Glu	Val	Pro	Leu	Ala	Glu	Ala	Ile	Pro	
2035					2040					2045					

ttg gct gat cag cca cat ctg ttg cag cca aat gct aga aag gag Leu Ala Asp Gln Pro His Leu Leu Gln Pro Asn Ala Arg Lys Glu 2050 2055 2060	6225
gat ctt ttt ggc cgt cca agt cag ggt ctt tat tct tca tct gcc Asp Leu Phe Gly Arg Pro Ser Gln Gly Leu Tyr Ser Ser Ser Ala 2065 2070 2075	6270
agt agt ggg aaa tgt tta atg gag gtt aca gtg gat aga aac tgc Ser Ser Gly Lys Cys Leu Met Glu Val Thr Val Asp Arg Asn Cys 2080 2085 2090	6315
cta gag gtt ctt cca aca aaa atg tct tat gct gcc aat ctg aaa Leu Glu Val Leu Pro Thr Lys Met Ser Tyr Ala Ala Asn Leu Lys 2095 2100 2105	6360
aat gta atg aac atg caa aac cgg caa aaa aaa gaa ggg gaa gaa Asn Val Met Asn Met Gln Asn Arg Gln Lys Lys Glu Gly Glu Glu 2110 2115 2120	6405
cag ccc gtg ctg cca gaa gaa act gag agt tca aaa cca ggg cca Gln Pro Val Leu Pro Glu Glu Thr Glu Ser Ser Lys Pro Gly Pro 2125 2130 2135	6450
tct gct cat gat ctt gct gca caa tta aaa agt agc tta cta gca Ser Ala His Asp Leu Ala Ala Gln Leu Lys Ser Ser Leu Leu Ala 2140 2145 2150	6495
gaa ata gga ctt act gaa agt gaa ggg cca cct ctc aca tct ttc Glu Ile Gly Leu Thr Glu Ser Glu Gly Pro Pro Leu Thr Ser Phe 2155 2160 2165	6540
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aaa Lys 2320	ggc Gly 2320	acc Thr 2320	cac His 2325	aca Thr 2325	agt Ser 2325	tta Leu 2330	atg Met 2330	cag Gln 2330	aga Arg 2330	tta Leu 2330	agg Arg 2330	aac Asn 2330	cga Arg 2330	gga Gly 2330	7035
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Met	Tyr	Glu	Ser	Leu	Arg	Gln	Leu	Ile	Leu	Ala	Ser	Gln	Ser	Ser	
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Val	Arg	Lys	Tyr	Ala	Glu	His	Arg	Met	Leu	Val	Val	Ala	Glu	Gln	
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Asn	Gly	Cys	Gly	Glu	Val	Asn	Val	Gln	Met	Leu	Ile	Ser	Phe	Thr	
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Ser	Phe	Asn	Asp	Glu	Ser	Gly	Glu	Asn	Ala	Glu	Lys	Leu	Leu	Gln	
2695					2700					2705					
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Phe	Lys	Arg	Trp	Phe	Trp	Ser	Ile	Val	Glu	Lys	Met	Ser	Met	Thr	
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Glu	Arg	Gln	Asp	Leu	Val	Tyr	Phe	Trp	Thr	Ser	Ser	Pro	Ser	Leu	
2725					2730					2735					
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Pro	Ala	Ser	Glu	Glu	Gly	Phe	Gln	Pro	Met	Pro	Ser	Ile	Thr	Ile	
2740					2745					2750					
aga	cca	cca	gat	gac	caa	cat	ctt	cct	act	gca	aat	act	tgc	att	8340
Arg	Pro	Pro	Asp	Asp	Gln	His	Leu	Pro</							

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<212> PRT

<213> NM_015902 EDD, hyperplastic discs protein, DD5

<400> 64

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Lys Gln Cys Val Val Gly Pro Asn His Ala Ala Phe Leu Leu Glu Asp
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Gly Arg Val Cys Arg Ile Gly Phe Ser Val Gln Pro Asp Arg Leu Glu
65 70 75 80

Leu Gly Lys Pro Asp Asn Asn Asp Gly Ser Lys Leu Asn Ser Asn Ser
85 90 95

Gly Ala Gly Arg Thr Ser Arg Pro Gly Arg Thr Ser Asp Ser Pro Trp
100 105 110

Phe Leu Ser Gly Ser Glu Thr Leu Gly Arg Leu Ala Gly Asn Thr Leu
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Gly Ser Arg Trp Ser Ser Gly Val Gly Gly Ser Gly Gly Gly Ser Ser
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Gly Arg Ser Ser Ala Gly Ala Arg Asp Ser Arg Arg Gln Thr Arg Val
145 150 155 160

Ile Arg Thr Gly Arg Asp Arg Gly Ser Gly Leu Leu Gly Ser Gln Pro
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Gln Pro Val Ile Pro Ala Ser Val Ile Pro Glu Glu Leu Ile Ser Gln
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Ala Gln Val Val Leu Gln Gly Lys Ser Arg Ser Val Ile Ile Arg Glu
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Leu Gln Arg Thr Asn Leu Asp Val Asn Leu Ala Val Asn Asn Leu Leu
 210 215 220

Ser Arg Asp Asp Glu Asp Gly Asp Asp Gly Asp Asp Thr Ala Ser Glu
 225 230 235 240

Ser Tyr Leu Pro Gly Glu Asp Leu Met Ser Leu Leu Asp Ala Asp Ile
 245 250 255

His Ser Ala His Pro Ser Val Ile Ile Asp Ala Asp Ala Met Phe Ser
 260 265 270

Glu Asp Ile Ser Tyr Phe Gly Tyr Pro Ser Phe Arg Arg Ser Ser Leu
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Ser Arg Leu Gly Ser Ser Arg Val Leu Leu Leu Pro Leu Glu Arg Asp
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Ser Glu Leu Leu Arg Glu Arg Glu Ser Val Leu Arg Leu Arg Glu Arg
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Arg Trp Leu Asp Gly Ala Ser Phe Asp Asn Glu Arg Gly Ser Thr Ser
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Lys Glu Gly Glu Pro Asn Leu Asp Lys Lys Asn Thr Pro Val Gln Ser
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Pro Val Ser Leu Gly Glu Asp Leu Gln Trp Trp Pro Asp Lys Asp Gly
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Thr Lys Phe Ile Cys Ile Gly Ala Leu Tyr Ser Glu Leu Leu Ala Val
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Ser Ser Lys Gly Glu Leu Tyr Gln Trp Lys Trp Ser Glu Ser Glu Pro
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Tyr Arg Asn Ala Gln Asn Pro Ser Leu His His Pro Arg Ala Thr Phe
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Leu Gly Leu Thr Asn Glu Lys Ile Val Leu Leu Ser Ala Asn Ser Ile
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Arg Ala Thr Val Ala Thr Glu Asn Asn Lys Val Ala Thr Trp Val Asp
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Glu Thr Leu Ser Ser Val Ala Ser Lys Leu Glu His Thr Ala Gln Thr
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Tyr Ser Glu Leu Gln Gly Glu Arg Ile Val Ser Leu His Cys Cys Ala
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Leu Tyr Thr Cys Ala Gln Leu Glu Asn Ser Leu Tyr Trp Trp Gly Val
 485 490 495

Val Pro Phe Ser Gln Arg Lys Lys Met Leu Glu Lys Ala Arg Ala Lys
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Asn Lys Lys Pro Lys Ser Ser Ala Gly Ile Ser Ser Met Pro Asn Ile
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Gly Ala Val Ala Phe Ser Ile Ser Ala Gly Ile Pro Lys Val Gly Val
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Arg Ser Pro Glu Ser Leu Lys Asn Met Glu Lys Ala Ser Lys Thr Thr
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Glu Ala Lys Pro Glu Ser Lys Gln Glu Pro Val Lys Thr Glu Met Gly
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Pro Pro Pro Ser Pro Ala Ser Thr Cys Ser Asp Ala Ser Ser Ile Ala
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Lys Glu Glu Glu Lys Val Asn Glu Glu Gln Trp Ser Leu Arg Glu Val
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Val Phe Val Glu Asp Val Lys Asn Val Pro Val Gly Lys Val Leu Lys
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Val Asp Gly Ala Tyr Val Ala Val Lys Phe Pro Gly Thr Ser Ser Asn
 675 680 685

Thr Asn Cys Gln Asn Ser Ser Gly Pro Asp Ala Asp Pro Ser Ser Leu
 690 695 700

Leu Gln Asp Cys Arg Leu Leu Arg Ile Asp Glu Leu Gln Val Val Lys
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Thr Gly Gly Thr Pro Lys Val Pro Asp Cys Phe Gln Arg Thr Pro Lys
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Lys Leu Cys Ile Pro Glu Lys Thr Glu Ile Leu Ala Val Asn Val Asp
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Ser Lys Gly Val His Ala Val Leu Lys Thr Gly Asn Trp Val Arg Tyr
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Cys Ile Phe Asp Leu Ala Thr Gly Lys Ala Glu Gln Glu Asn Asn Phe
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Pro Thr Ser Ser Ile Ala Phe Leu Gly Gln Asn Glu Arg Asn Val Ala
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Ile Phe Thr Ala Gly Gln Glu Ser Pro Ile Ile Leu Arg Asp Gly Asn
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Gly Thr Ile Tyr Pro Met Ala Lys Asp Cys Met Gly Gly Ile Arg Asp
 820 825 830

Pro Asp Trp Leu Asp Leu Pro Pro Ile Ser Ser Leu Gly Met Gly Val
 835 840 845

His Ser Leu Ile Asn Leu Pro Ala Asn Ser Thr Ile Lys Lys Lys Ala
 850 855 860

Ala Val Ile Ile Met Ala Val Glu Lys Gln Thr Leu Met Gln His Ile
 865 870 875 880

Leu Arg Cys Asp Tyr Glu Ala Cys Arg Gln Tyr Leu Met Asn Leu Glu
 885 890 895

Gln Ala Val Val Leu Glu Gln Asn Leu Gln Met Leu Gln Thr Phe Ile
 900 905 910

Ser His Arg Cys Asp Gly Asn Arg Asn Ile Leu His Ala Cys Val Ser
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Val Cys Phe Pro Thr Ser Asn Lys Glu Thr Lys Glu Glu Glu Glu Ala
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Glu Arg Ser Glu Arg Asn Thr Phe Ala Glu Arg Leu Ser Ala Val Glu
 945 950 955 960

Ala Ile Ala Asn Ala Ile Ser Val Val Ser Ser Asn Gly Pro Gly Asn
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Arg Ala Gly Ser Ser Ser Arg Ser Leu Arg Leu Arg Glu Met Met
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Arg Arg Ser Leu Arg Ala Ala Gly Leu Gly Arg His Glu Ala Gly Ala
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Ile Asp Phe Ile Leu Ala Pro Ala Val Gly Ser Leu Thr Thr Ala
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Asn Ala His Phe Ile Leu Lys Leu Leu Cys Asp Ser Val Val Leu
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Gln Pro Tyr Leu Arg Glu Leu Leu Ser Ala Lys Asp Ala Arg Gly
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Met Thr Pro Phe Met Ser Ala Val Ser Gly Arg Ala Tyr Pro Ala
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Ile Ser Ser Ser Glu Lys Glu Glu Asp Val Phe Met Gly Met Val
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His Asp Cys Lys Leu Lys Arg Thr Ser Pro Thr Ala Tyr Cys Asp
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Cys Trp Glu Lys Cys Lys Cys Lys Thr Leu Ile Ala Gly Gln Lys

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Leu Val Gln Thr Val Ala Arg Gln Thr Val Glu His Cys Gln Tyr 1280 1285 1290		
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Pro Glu Asp Ser Asp Met Pro Asp His Asp Leu Glu Pro Pro Arg 1310 1315 1320		
Phe Ala Gln Leu Ala Leu Glu Arg Val Leu Gln Asp Trp Asn Ala 1325 1330 1335		
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Val Tyr Leu Asn Gln Gln Ser Gly Thr Ile Arg Leu Asp Cys Phe 1370 1375 1380		
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Glu Leu Cys Asn Val Ala Glu Ser Leu Ile Val Pro Val Arg Met 1475 1480 1485		

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 Asp Pro Gly His Pro Asn His Pro Leu His Ala Ser Gln Asn Ser
 1865 1870 1875
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 1880 1885 1890
 Thr Leu Glu Gly Arg Arg Arg Ala Thr Leu Leu Ser Ala Arg Gln
 1895 1900 1905
 Gly Met Met Ser Ala Arg Gly Asp Phe Leu Asn Tyr Ala Leu Ser
 1910 1915 1920
 Leu Met Arg Ser His Asn Asp Glu His Ser Asp Val Leu Pro Val
 1925 1930 1935
 Leu Asp Val Cys Ser Leu Lys His Val Ala Tyr Val Phe Gln Ala
 1940 1945 1950
 Leu Ile Tyr Trp Ile Lys Ala Met Asn Gln Gln Thr Thr Leu Asp
 1955 1960 1965
 Thr Pro Gln Leu Glu Arg Lys Arg Thr Arg Glu Leu Leu Glu Leu
 1970 1975 1980
 Gly Ile Asp Asn Glu Asp Ser Glu His Glu Asn Asp Asp Asp Thr
 1985 1990 1995

Asn Gln Ser Ala Thr Leu Asn Asp Lys Asp Asp Asp Ser Leu Pro
 2000 2005 2010

Ala Glu Thr Gly Gln Asn His Pro Phe Phe Arg Arg Ser Asp Ser
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 Ile Ile Ala His Gly Arg Glu Asn Gly Ala Asp Ser Ile Leu Asp
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 Lys Arg His Gly Ser Ser Arg Ser Val Val Asp Met Asp Leu Asp
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 Gln Asn Val Tyr Glu Tyr Val Arg Lys Tyr Ala Glu His Arg Met
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 Met Pro Ser Ile Thr Ile Arg Pro Pro Asp Asp Gln His Leu Pro
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Thr Ala Asn Thr Cys Ile Sér Arg Leu Tyr Val Pro Leu Tyr Ser
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cagcc atg gcc cca aga aag aga ggt gga cga ggt att tca ttc atc ttt 170
Met Ala Pro Arg Lys Arg Gly Gly Arg Gly Ile Ser Phe Ile Phe
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Cys Cys Phe Arg Asn Asn Asp His Pro Glu Ile Thr Tyr Arg Leu Arg
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Asn Asp Ser Asn Phe Ala Leu Gln Thr Met Glu Pro Ala Leu Pro Met
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Pro Pro Val Glu Glu Leu Asp Val Met Phe Ser Glu Leu Val Asp Glu
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Leu Asp Leu Thr Asp Lys His Arg Glu Ala Met Phe Ala Leu Pro Ala
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gag aaa aaa tgg caa ata tac tgt agc aag aaa aag gac cag gaa gaa 410
Glu Lys Lys Trp Gln Ile Tyr Cys Ser Lys Lys Lys Asp Gln Glu Glu
80 85 90 95
aac aag gga gct aca agt tgg cct gaa ttc tac att gat cag ctc aat 458
Asn Lys Gly Ala Thr Ser Trp Pro Glu Phe Tyr Ile Asp Gln Leu Asn
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Ser Met Ala Ala Arg Lys Ser Leu Leu Ala Leu Glu Lys Glu Glu Glu

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cga ata cat act tct ctc att ggc tgt ata aag gcg tta atg aac aac Arg Ile His Thr Ser Leu Ile Gly Cys Ile Lys Ala Leu Met Asn Asn 180 185 190			698
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cct gaa aaa agt gac att gac cta ttg gag gaa cat aaa cac gaa ctg Pro Glu Lys Ser Asp Ile Asp Leu Leu Glu Glu His Lys His Glu Leu 740 745 750			2378
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Ile Leu Asn Phe Leu Lys Thr Met Asp Tyr Glu Thr Ser Glu Ser Arg
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Ile His Thr Ser Leu Ile Gly Cys Ile Lys Ala Leu Met Asn Asn Ser
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Gln Gly Arg Ala His Val Leu Ala His Ser Glu Ser Ile Asn Val Ile
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Ala Gln Ser Leu Ser Thr Glu Asn Ile Lys Thr Lys Val Ala Val Leu
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Glu Ile Leu Gly Ala Val Cys Leu Val Pro Gly Gly His Lys Lys Val
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Phe Gln Thr Leu Ile Asn Asp Leu Asp Lys Ser Thr Gly Arg Tyr Arg
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Arg Tyr Glu Phe Leu Met Leu Gly Ile Gln Pro Val Ile Asp Lys Leu
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Arg Glu His Glu Asn Ser Thr Leu Asp Arg His Leu Asp Phe Phe Glu
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Met Leu Arg Asn Glu Asp Glu Leu Glu Phe Ala Lys Arg Phe Glu Leu
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Val His Ile Asp Thr Lys Ser Ala Thr Gln Met Phe Glu Leu Thr Arg
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Lys Arg Leu Thr His Ser Glu Ala Tyr Pro His Phe Met Ser Ile Leu
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His His Cys Leu Gln Met Pro Tyr Lys Arg Ser Gly Asn Thr Val Gln
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Tyr Trp Leu Leu Leu Asp Arg Ile Ile Gln Gln Ile Val Ile Gln Asn
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Lys Asn Val Val Arg Met Leu Val Asn Glu Asn Glu Val Lys Gln Trp
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Lys Glu Gln Ala Glu Lys Met Arg Lys Glu His Asn Glu Leu Gln Gln
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565 570 575

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580 585 590

Pro Met Gly Leu Ala Leu Lys Lys Lys Ser Ile Pro Gln Pro Thr Asn
595 600 605

Ala Leu Lys Ser Phe Asn Trp Ser Lys Leu Pro Glu Asn Lys Leu Glu
610 615 620

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660 665 670

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740 745 750

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 Tyr Gly Phe Lys Ile Ser Ser Leu Asn Lys Ile Ala Asp Thr Lys Ser
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1030

1035

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 Ser Cys Gly Val Asn Leu Tyr Gln Phe Tyr Gly Pro Ser Gly Gln Tyr
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acc cat gaa ttt gat gga gat gag cag ttc tac gtg gac ctg gag agg 192
 Thr His Glu Phe Asp Gly Asp Glu Gln Phe Tyr Val Asp Leu Glu Arg
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 Lys Glu Thr Ala Trp Arg Trp Pro Glu Phe Ser Lys Phe Gly Gly Phe
 65 70 75 80

gac ccg cag ggt gca ctg aga aac atg gct gtg gca aaa cac aac ttg 288
 Asp Pro Gln Gly Ala Leu Arg Asn Met Ala Val Ala Lys His Asn Leu
 85 90 95

aac atc atg att aaa cgc tac aac tct acc gct gct acc aat gag gtt 336
 Asn Ile Met Ile Lys Arg Tyr Asn Ser Thr Ala Ala Thr Asn Glu Val
 100 105 110

cct gag gtc aca gtg ttt tcc aag tct ccc gtg aca ctg ggt cag ccc 384
 Pro Glu Val Thr Val Phe Ser Lys Ser Pro Val Thr Leu Gly Gln Pro
 115 120 125

aac acc ctc att tgt ctt gtg gac aac atc ttt cct cct.gtg gtc aac 432
 Asn Thr Leu Ile Cys Leu Val Asp Asn Ile Phe Pro Pro Val Val Asn
 130 135 140
 atc aca tgg ctg agc aat ggg cag tca gtc aca gaa ggt gtt tct gag 480
 Ile Thr Trp Leu Ser Asn Gly Gln Ser Val Thr Glu Gly Val Ser Glu
 145 150 155 160
 acc agc ttc ctc tcc aag agt gat cat tcc ttc ttc aag atc agt tac 528
 Thr Ser Phe Leu Ser Lys Ser Asp His Ser Phe Phe Lys Ile Ser Tyr
 165 170 175
 ctc acc ttc ctc cct tct gct gat gag att tat gac tgc aag gtg gag 576
 Leu Thr Phe Leu Pro Ser Ala Asp Glu Ile Tyr Asp Cys Lys Val Glu
 180 185 190
 cac tgg ggc ctg gac cag cct ctt ctg aaa cac tgg gag cct gag att 624
 His Trp Gly Leu Asp Gln Pro Leu Leu Lys His Trp Glu Pro Glu Ile
 195 200 205
 cca gcc cct atg tca gag ctc aca gag act gtg gtc tgt gcc ctg ggg 672
 Pro Ala Pro Met Ser Glu Leu Thr Glu Thr Val Val Cys Ala Leu Gly
 210 215 220
 ttg tct gtg ggc ctc atg ggc att gtg gtg ggc act gtc ttc atc atc 720
 Leu Ser Val Gly Leu Met Gly Ile Val Val Gly Thr Val Phe Ile Ile
 225 230 235 240
 caa ggc ctg cgt tca gtt ggt gct tcc aga cac caa ggg cca ttg 765
 Gln Gly Leu Arg Ser Val Gly Ala Ser Arg His Gln Gly Pro Leu
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<212> PRT

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 20 25 30

Ser Cys Gly Val Asn Leu Tyr Gln Phe Tyr Gly Pro Ser Gly Gln Tyr
 35 40 45

Thr His Glu Phe Asp Gly Asp Glu Gln Phe Tyr Val Asp Leu Glu Arg
50 55 60

Lys Glu Thr Ala Trp Arg Trp Pro Glu Phe Ser Lys Phe Gly Gly Phe
65 70 75 80

Asp Pro Gln Gly Ala Leu Arg Asn Met Ala Val Ala Lys His Asn Leu
85 90 95

Asn Ile Met Ile Lys Arg Tyr Asn Ser Thr Ala Ala Thr Asn Glu Val
100 105 110

Pro Glu Val Thr Val Phe Ser Lys Ser Pro Val Thr Leu Gly Gln Pro
115 120 125

Asn Thr Leu Ile Cys Leu Val Asp Asn Ile Phe Pro Pro Val Val Asn
130 135 140

Ile Thr Trp Leu Ser Asn Gly Gln Ser Val Thr Glu Gly Val Ser Glu
145 150 155 160

Thr Ser Phe Leu Ser Lys Ser Asp His Ser Phe Phe Lys Ile Ser Tyr
165 170 175

Leu Thr Phe Leu Pro Ser Ala Asp Glu Ile Tyr Asp Cys Lys Val Glu
180 185 190

His Trp Gly Leu Asp Gln Pro Leu Leu Lys His Trp Glu Pro Glu Ile
195 200 205

Pro Ala Pro Met Ser Glu Leu Thr Glu Thr Val Val Cys Ala Leu Gly
210 215 220

Leu Ser Val Gly Leu Met Gly Ile Val Val Gly Thr Val Phe Ile Ile
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Gln Gly Leu Arg Ser Val Gly Ala Ser Arg His Gln Gly Pro Leu
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<210> 69

<211> 2820

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 atg ttc ctc tcc atc cta gtg gcg ctg tgc ctg tgg ctg cac ctg gcg 285
 Met Phe Leu Ser Ile Leu Val Ala Leu Cys Leu Trp Leu His Leu Ala
 1 5 10 15
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 Leu Gly Val Arg Gly Ala Pro Cys Glu Ala Val Arg Ile Pro Met Cys
 20 25 30
 cgg cac atg ccc tgg aac atc acg cgg atg ccc aac cac ctg cac cac 381
 Arg His Met Pro Trp Asn Ile Thr Arg Met Pro Asn His Leu His His
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 agc acg cag gag aac gcc atc ctg gcc atc gag cag tac gag gag ctg 429
 Ser Thr Gln Glu Asn Ala Ile Leu Ala Ile Glu Gln Tyr Glu Glu Leu
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 Val Asp Val Asn Cys Ser Ala Val Leu Arg Phe Phe Phe Cys Ala Met
 65 70 75 80
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 Tyr Ala Pro Ile Cys Thr Leu Glu Phe Leu His Asp Pro Ile Lys Pro
 85 90 95
 tgc aag tcg gtg tgc caa cgc gcg cgc gac gac tgc gag ccc ctc atg 573
 Cys Lys Ser Val Cys Gln Arg Ala Arg Asp Asp Cys Glu Pro Leu Met
 100 105 110
 aag atg tac aac cac agc tgg ccc gaa agc ctg gcc tgc gac gag ctg 621
 Lys Met Tyr Asn His Ser Trp Pro Glu Ser Leu Ala Cys Asp Glu Leu
 115 120 125
 cct gtc tat gac cgt ggc gtg tgc att tcg cct gaa gcc atc gtc acg 669
 Pro Val Tyr Asp Arg Gly Val Cys Ile Ser Pro Glu Ala Ile Val Thr
 130 135 140
 gac ctc ccg gag gat gtt aag tgg ata gac atc aca cca gac atg atg 717
 Asp Leu Pro Glu Asp Val Lys Trp Ile Asp Ile Thr Pro Asp Met Met
 145 150 155 160
 gta cag gaa agg cct ctt gat gtt gac tgt aaa cgc cta agc ccc gat 765
 Val Gln Glu Arg Pro Leu Asp Val Asp Cys Lys Arg Leu Ser Pro Asp
 165 170 175
 cgg tgc aag tgt aaa aag gtg aag cca act ttg gca acg tat ctc agc 813
 Arg Cys Lys Cys Lys Lys Val Lys Pro Thr Leu Ala Thr Tyr Leu Ser
 180 185 190
 aaa aac tac agc tat gtt att cat gcc aaa ata aaa gct gtg cag agg 861
 Lys Asn Tyr Ser Tyr Val Ile His Ala Lys Ile Lys Ala Val Gln Arg
 195 200 205
 agt ggc tgc aat gag gtc aca acg gtg gtg gat gta aaa gag atc ttc 909

Ser	Gly	Cys	Asn	Glu	Val	Thr	Val	Val	Asp	Val	Lys	Glu	Ile	Phe		
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Lys	Ser	Ser	Ser	Pro	Ile	Pro	Arg	Thr	Gln	Val	Pro	Leu	Ile	Thr	Asn	
225				230						235					240	
tct	tct	tgc	cag	tgt	cca	cac	atc	ctg	ccc	cat	caa	gat	gtt	ctc	atc	1005
Ser	Ser	Cys	Gln	Cys	Pro	His	Ile	Leu	Pro	His	Gln	Asp	Val	Leu	Ile	
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Val	Glu	Lys	Trp	Arg	Asp	Gln	Leu	Ser	Lys	Arg	Ser	Ile	Gln	Trp	Glu	
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Glu	Arg	Leu	Gln	Glu	Gln	Arg	Arg	Thr	Val	Gln	Asp	Lys	Lys	Lys	Thr	
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gcc	ggg	cgc	acc	agt	cgt	agt	aat	ccc	ccc	aaa	cca	aag	gga	aag	cct	1197
Ala	Gly	Arg	Thr	Ser	Arg	Ser	Asn	Pro	Pro	Lys	Pro	Lys	Gly	Lys	Pro	
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cct	gct	ccc	aaa	cca	gcc	agt	ccc	aag	aag	aac	att	aaa	act	agg	agt	1245
Pro	Ala	Pro	Lys	Pro	Ala	Ser	Pro	Lys	Lys	Asn	Ile	Lys	Thr	Arg	Ser	
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gcc	cag	aag	aga	aca	aac	ccg	aaa	aga	gtg	tgagctaa	act	agtttccaaa				1295
Ala	Gln	Lys	Arg	Thr	Asn	Pro	Lys	Arg	Val							
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tatgtgttta	tggtctgcag	aaggatt	ttt	gtgatg	aaag	gggatttt	ttt	gaaaaatt	ag							1835
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gacagttggg atactttaat cagaaaaaaa gaacttattt gcagcatttt atcaacaaat 2375
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 aacctgtata catgtgtttc ataacctgcc tcctttgctt ggccttttat tgagataagt 2675
 tttcctgtca agaaagcaga aaccatctca tttctaacag ctgtgttata ttccatagta 2735
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<211> 346

<212> PRT

<213> NM_003014 SFRP4, secreted frizzled-related protein 4

<400> 70

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 20 25 30

Arg His Met Pro Trp Asn Ile Thr Arg Met Pro Asn His Leu His His
 35 40 45

Ser Thr Gln Glu Asn Ala Ile Leu Ala Ile Glu Gln Tyr Glu Glu Leu
 50 55 60

Val Asp Val Asn Cys Ser Ala Val Leu Arg Phe Phe Phe Cys Ala Met
 65 70 75 80

Tyr Ala Pro Ile Cys Thr Leu Glu Phe Leu His Asp Pro Ile Lys Pro
 85 90 95

Cys Lys Ser Val Cys Gln Arg Ala Arg Asp Asp Cys Glu Pro Leu Met
 100 105 110

Lys Met Tyr Asn His Ser Trp Pro Glu Ser Leu Ala Cys Asp Glu Leu
 115 120 125

Pro Val Tyr Asp Arg Gly Val Cys Ile Ser Pro Glu Ala Ile Val Thr
 130 135 140

Asp Leu Pro Glu Asp Val Lys Trp Ile Asp Ile Thr Pro Asp Met Met
 145 150 155 160
 Val Gln Glu Arg Pro Leu Asp Val Asp Cys Lys Arg Leu Ser Pro Asp
 165 170 175
 Arg Cys Lys Cys Lys Lys Val Lys Pro Thr Leu Ala Thr Tyr Leu Ser
 180 185 190
 Lys Asn Tyr Ser Tyr Val Ile His Ala Lys Ile Lys Ala Val Gln Arg
 195 200 205
 Ser Gly Cys Asn Glu Val Thr Thr Val Val Asp Val Lys Glu Ile Phe
 210 215 220
 Lys Ser Ser Ser Pro Ile Pro Arg Thr Gln Val Pro Leu Ile Thr Asn
 225 230 235 240
 Ser Ser Cys Gln Cys Pro His Ile Leu Pro His Gln Asp Val Leu Ile
 245 250 255
 Met Cys Tyr Glu Trp Arg Ser Arg Met Met Leu Leu Glu Asn Cys Leu
 260 265 270
 Val Glu Lys Trp Arg Asp Gln Leu Ser Lys Arg Ser Ile Gln Trp Glu
 275 280 285
 Glu Arg Leu Gln Glu Gln Arg Arg Thr Val Gln Asp Lys Lys Lys Thr
 290 295 300
 Ala Gly Arg Thr Ser Arg Ser Asn Pro Pro Lys Pro Lys Gly Lys Pro
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<213> NM_004039 annexin A2

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Val His Glu Ile Leu Cys Lys Leu Ser Leu Glu Gly Asp His Ser Thr
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ccc cca agt gca tat ggg tct gtc aaa gcc tat act aac ttt gat gct      154
Pro Pro Ser Ala Tyr Gly Ser Val Lys Ala Tyr Thr Asn Phe Asp Ala
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gag cgg gat gct ttg aac att gaa aca gcc atc aag acc aaa ggt gtg 202
Glu Arg Asp Ala Leu Asn Ile Glu Thr Ala Ile Lys Thr Lys Gly Val
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gat gag gtc acc att gtc aac att ttg acc aac cgc agc aat gca cag 250
Asp Glu Val Thr Ile Val Asn Ile Leu Thr Asn Arg Ser Asn Ala Gln
55 60 65

aga cag gat att gcc ttc gcc tac cag aga agg acc aaa aag gaa ctt 298
Arg Gln Asp Ile Ala Phe Ala Tyr Gln Arg Arg Thr Lys Lys Glu Leu
70 75 80

gca tca gca ctg aag tca gcc tta tct ggc cac ctg gag acg gtg att 346
Ala Ser Ala Leu Lys Ser Ala Leu Ser Gly His Leu Glu Thr Val Ile
85 90 95

ttg ggc cta ttg aag aca cct gct cag tat gac gct tct gag cta aaa 394
Leu Gly Leu Leu Lys Thr Pro Ala Gln Tyr Asp Ala Ser Glu Leu Lys
100 105 110 115

gct tcc atg aag ggg ctg gga acc gac gag gac tct ctc att gag atc 442
Ala Ser Met Lys Gly Leu Gly Thr Asp Glu Asp Ser Leu Ile Glu Ile
120 125 130

atc tgc tcc aga acc aac cag gag ctg cag gaa att aac aga gtc tac 490
Ile Cys Ser Arg Thr Asn Gln Glu Leu Gln Glu Ile Asn Arg Val Tyr
135 140 145

aag gaa atg tac aag act gat ctg gag aag gac att att tcg gac aca 538
Lys Glu Met Tyr Lys Thr Asp Leu Glu Lys Asp Ile Ile Ser Asp Thr
150 155 160

tct ggt gac ttc cgc aag ctg atg gtt gcc ctg gca aag ggt aga aga 586
Ser Gly Asp Phe Arg Lys Leu Met Val Ala Leu Ala Lys Gly Arg Arg
165 170 175

gca gag gat ggc tct gtc att gat tat gaa ctg att gac caa gat gct 634
Ala Glu Asp Gly Ser Val Ile Asp Tyr Glu Leu Ile Asp Gln Asp Ala
180 185 190 195

cgg gat ctc tat gac gct gga gtg aag agg aaa gga act gat gtt ccc 682
 Arg Asp Leu Tyr Asp Ala Gly Val Lys Arg Lys Gly Thr Asp Val Pro
 200 205 210

aag tgg atc agc atc atg acc gag cgg agc gtg ccc cac ctc cag aaa 730
Lys Trp Ile Ser Ile Met Thr Glu Arg Ser Val Pro His Leu Gln Lys
215 220 225

gta ttt gat agg tac aag agt tac agc cct tat gac atg ttg gaa agc 778
Val Phe Asp Arg Tyr Lys Ser Tyr Ser Pro Tyr Asp Met Leu Glu Ser
230 235 240

atc agg aaa gag gtt aaa gga gac ctg gaa aat gct ttc ctg aac ctg 826
 Ile Arg Lys Glu Val Lys Gly Asp Leu Glu Asn Ala Phe Leu Asn Leu
 245 250 255

gtt cag tgc att cag aac aag ccc ctg tat ttt gct gat cgg ctg tat 874
 Val Gln Cys Ile Gln Asn Lys Pro Leu Tyr Phe Ala Asp Arg Leu Tyr
 260 265 270 275

gac tcc atg aag ggc aag ggg acg cga gat aag gtc ctg atc aga atc 922
 Asp Ser Met Lys Gly Lys Gly Thr Arg Asp Lys Val Leu Ile Arg Ile
 280 285 290

atg gtc tcc cgc agt gaa gtg gac atg ttg aaa att agg tct gaa ttc 970
 Met Val Ser Arg Ser Glu Val Asp Met Leu Lys Ile Arg Ser Glu Phe
 295 300 305

aag aga aag tac ggc aag tcc ctg tac tat tat atc cag caa gac act 1018
 Lys Arg Lys Tyr Gly Lys Ser Leu Tyr Tyr Tyr Ile Gln Gln Asp Thr
 310 315 320

aag ggc gac tac cag aaa gcg ctg ctg tac ctg tgt ggt gga gat gac 1066
 Lys Gly Asp Tyr Gln Lys Ala Leu Leu Tyr Leu Cys Gly Gly Asp Asp
 325 330 335

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cctgtaagcc aaagaaatga acattccaag gagttggaag tgaagtctat gatgtgaaac 1306

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<212> PRT

<213> NM_004039 annexin A2

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Phe Asp Ala Glu Arg Asp Ala Leu Asn Ile Glu Thr Ala Ile Lys Thr
 35 40 45

Lys Gly Val Asp Glu Val Thr Ile Val Asn Ile Leu Thr Asn Arg Ser
 50 55 60

Asn Ala Gln Arg Gln Asp Ile Ala Phe Ala Tyr Gln Arg Arg Thr Lys
 65 70 75 80

Lys Glu Leu Ala Ser Ala Leu Lys Ser Ala Leu Ser Gly His Leu Glu
85 90 95

Thr Val Ile Leu Gly Leu Leu Lys Thr Pro Ala Gln Tyr Asp Ala Ser
100 105 110

Glu Leu Lys Ala Ser Met Lys Gly Leu Gly Thr Asp Glu Asp Ser Leu
115 120 125

Ile Glu Ile Ile Cys Ser Arg Thr Asn Gln Glu Leu Gln Glu Ile Asn
130 135 140

Arg Val Tyr Lys Glu Met Tyr Lys Thr Asp Leu Glu Lys Asp Ile Ile
145 150 155 160

Ser Asp Thr Ser Gly Asp Phe Arg Lys Leu Met Val Ala Leu Ala Lys
165 170 175

Gly Arg Arg Ala Glu Asp Gly Ser Val Ile Asp Tyr Glu Leu Ile Asp
180 185 190

Gln Asp Ala Arg Asp Leu Tyr Asp Ala Gly Val Lys Arg Lys Gly Thr
195 200 205

Asp Val Pro Lys Trp Ile Ser Ile Met Thr Glu Arg Ser Val Pro His
210 215 220

Leu Gln Lys Val Phe Asp Arg Tyr Lys Ser Tyr Ser Pro Tyr Asp Met
225 230 235 240

Leu Glu Ser Ile Arg Lys Glu Val Lys Gly Asp Leu Glu Asn Ala Phe
245 250 255

Leu Asn Leu Val Gln Cys Ile Gln Asn Lys Pro Leu Tyr Phe Ala Asp
260 265 270

Arg Leu Tyr Asp Ser Met Lys Gly Lys Gly Thr Arg Asp Lys Val Leu
275 280 285

Ile Arg Ile Met Val Ser Arg Ser Glu Val Asp Met Leu Lys Ile Arg
290 295 300

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 Met Val Thr
 1
 cac agc aag ttt ccc gcc gcc ggg atg agc cgc ccc ctg gac acc agc 163
 His Ser Lys Phe Pro Ala Ala Gly Met Ser Arg Pro Leu Asp Thr Ser
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 Leu Arg Leu Lys Thr Phe Ser Ser Lys Ser Glu Tyr Gln Leu Val Val
 20 25 30 35
 aac gca gtg cgc aag ctg cag gag agc ggc ttc tac tgg agc gca gtg 259
 Asn Ala Val Arg Lys Leu Gln Glu Ser Gly Phe Tyr Trp Ser Ala Val
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 Thr Gly Gly Glu Ala Asn Leu Leu Ser Ala Glu Pro Ala Gly Thr
 55 60 65
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 Phe Leu Ile Arg Asp Ser Ser Asp Gln Arg His Phe Thr Leu Ser
 70 75 80
 gtc aag acc cag tct ggg acc aag aac ctg cgc atc cag tgt gag ggg 403
 Val Lys Thr Gln Ser Gly Thr Lys Asn Leu Arg Ile Gln Cys Glu Gly
 85 90 95
 ggc agc ttc tct ctg cag agc gat ccc cgg agc acg cag ccc gtg ccc 451
 Gly Ser Phe Ser Leu Gln Ser Asp Pro Arg Ser Thr Gln Pro Val Pro
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 cgc ttc gac tgc gtg ctc aag ctg gtg tac cac tac atg ccg ccc cct 499
 Arg Phe Asp Cys Val Leu Lys Leu Val Tyr His Tyr Met Pro Pro Pro
 120 125 130
 gga gcc ccc tcc ttc ccc tcg cca cct act gaa ccc tcc tcc gag gtg 547
 Gly Ala Pro Ser Phe Pro Ser Pro Pro Thr Glu Pro Ser Ser Glu Val
 135 140 145
 ccc gag cag ccg tct gcc cag cca ctc cct ggg agt ccc ccc aga aga 595
 Pro Glu Gln Pro Ser Ala Gln Pro Leu Pro Gly Ser Pro Pro Arg Arg
 150 155 160
 gcc tat tac atc tac tcc ggg ggc gag aag atc ccc ctg gtg ttg agc 643

Ala Tyr Tyr Ile Tyr Ser Gly Gly Glu Lys Ile Pro Leu Val Leu Ser
 165 170 175

cgg ccc ctc tcc tcc aac gtg gcc act ctt cag cat ctc tgt cgg aag 691
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 180 185 190 195

acc gtc aac ggc cac ctg gac tcc tat gag aaa gtc acc cag ctg ccg 739
 Thr Val Asn Gly His Leu Asp Ser Tyr Glu Lys Val Thr Gln Leu Pro
 200 205 210

ggg ccc att cgg gag ttc ctg gac cag tac gat gcc ccg ctt 781
 Gly Pro Ile Arg Glu Phe Leu Asp Gln Tyr Asp Ala Pro Leu
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gtggcacat 850

<210> 74

<211> 225

<212> PRT

<213> NM_003955 SOCS3

<400> 74

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 35 40 45

Ser Ala Val Thr Gly Gly Glu Ala Asn Leu Leu Leu Ser Ala Glu Pro
 50 55 60

Ala Gly Thr Phe Leu Ile Arg Asp Ser Ser Asp Gln Arg His Phe Phe
 65 70 75 80

Thr Leu Ser Val Lys Thr Gln Ser Gly Thr Lys Asn Leu Arg Ile Gln
 85 90 95

Cys Glu Gly Gly Ser Phe Ser Leu Gln Ser Asp Pro Arg Ser Thr Gln
 100 105 110

Pro Val Pro Arg Phe Asp Cys Val Leu Lys Leu Val Tyr His Tyr Met
 115 120 125

Pro Pro Pro Gly Ala Pro Ser Phe Pro Ser Pro Pro Thr Glu Pro Ser
 130 135 140

Ser Glu Val Pro Glu Gln Pro Ser Ala Gln Pro Leu Pro Gly Ser Pro
145 150 155 160

Pro Arg Arg Ala Tyr Tyr Ile Tyr Ser Gly Gly Glu Lys Ile Pro Leu
165 170 175

Val Leu Ser Arg Pro Leu Ser Ser Asn Val Ala Thr Leu Gln His Leu
180 185 190

Cys Arg Lys Thr Val Asn Gly His Leu Asp Ser Tyr Glu Lys Val Thr
195 200 205

Gln Leu Pro Gly Pro Ile Arg Glu Phe Leu Asp Gln Tyr Asp Ala Pro
210 215 220

Leu
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<210> 75

<211> 369

<212> DNA

<213> NM_000331 SAA1, serum amyloid A1

<220>

<221> CDS

<222> (1)..(366)

<223>

<400> 75

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Met Lys Leu Leu Thr Gly Leu Val Phe Cys Ser Leu Val Leu Gly Val
1 5 10 15

agc agc cga agc ttc ttt tcg ttc ctt ggc gag gct ttt gat ggg gct 96
Ser Ser Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala
20 25 30

cgg gac atg tgg aga gcc tac tct gac atg aga gaa gcc aat tac atc 144
Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile
35 40 45

ggc tca gac aaa tac ttc cat gct cgg ggg aac tat gat gct gcc aaa 192
Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys
50 55 60

agg gga cct ggg ggt gtc tgg gct gca gaa gcg atc agc gat gcc aga 240
Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asp Ala Arg
65 70 75 80

gag aat atc cag aga ttc ttt gcc cat ggt gcg gag gac tcg ctg gct 288
Glu Asn Ile Gln Arg Phe Phe Gly His Gly Ala Glu Asp Ser Leu Ala
85 90 95

gat cag gct gcc aat gaa tgg ggc agg agt ggc aaa gac ccc aat cac 336
 Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His
 100 110

ttc cga cct gct ggc ctg cct gag aaa tac tga 369
 Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 115 120

<210> 76

<211> 122

<212> PRT

<213> NM_000331 SAA1, serum amyloid A1

<400> 76

Met Lys Leu Leu Thr Gly Leu Val Phe Cys Ser Leu Val Leu Gly Val
 1 10 15

Ser Ser Arg Ser Phe Phe Ser Phe Leu Gly Glu Ala Phe Asp Gly Ala
 20 25 30

Arg Asp Met Trp Arg Ala Tyr Ser Asp Met Arg Glu Ala Asn Tyr Ile
 35 40 45

Gly Ser Asp Lys Tyr Phe His Ala Arg Gly Asn Tyr Asp Ala Ala Lys
 50 55 60

Arg Gly Pro Gly Gly Val Trp Ala Ala Glu Ala Ile Ser Asp Ala Arg
 65 70 75 80

Glu Asn Ile Gln Arg Phe Phe Gly His Gly Ala Glu Asp Ser Leu Ala
 85 90 95

Asp Gln Ala Ala Asn Glu Trp Gly Arg Ser Gly Lys Asp Pro Asn His
 100 105 110

Phe Arg Pro Ala Gly Leu Pro Glu Lys Tyr
 115 120

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<211> 895

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<220>

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<223>

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cgcgcggggc	ccagctgagc	cgccctc	atg aag ccg ccc gcg gag gac ctg tcg			173
			Met Lys Pro Pro Ala Glu Asp Leu Ser			
		1		5		
gac gcg ctg tgc gag ttt gac gcg gtg ctg gcc gac ttc gcg tcg ccc						221
Asp Ala Leu Cys Glu Phe Asp Ala Val Leu Ala Asp Phe Ala Ser Pro						
10	15		20		25	
ttc cac gag cgc cac ttc cac tac gag gag cac ctg gag cgc atg aag						269
Phe His Glu Arg His Phe His Tyr Glu Glu His Leu Glu Arg Met Lys						
	30		35		40	
cgg cgc agc agc gcc agt gtc agc gac agc agc ggc ttc agc gac tcg						317
Arg Arg Ser Ser Ala Ser Val Ser Asp Ser Ser Gly Phe Ser Asp Ser						
	45		50		55	
gag agt gca gat tca ctt tat agg aac agc ttc agc ttc agt gat gaa						365
Glu Ser Ala Asp Ser Leu Tyr Arg Asn Ser Phe Ser Phe Ser Asp Glu						
	60		65		70	
aaa ctg aat tct cca aca gac tct acc cca gct ctt ctc tct gcc act						413
Lys Leu Asn Ser Pro Thr Asp Ser Thr Pro Ala Leu Leu Ser Ala Thr						
	75		80		85	
gtc act cct cag aaa gct aaa tta gga gac aca aaa gag cta gaa gcc						461
Val Thr Pro Gln Lys Ala Lys Leu Gly Asp Thr Lys Glu Leu Glu Ala						
	90		95		100	105
ttc att gct gat ctt gac aaa act tta gca agt atg tgaacaaga						507
Phe Ile Ala Asp Leu Asp Lys Thr Leu Ala Ser Met						
	110		115			
agttctgggt cctttcatca taaggggagaa gtttcagaaa gttccgagga cctgctaaaa						567
tcagctacta gaatctgctg ccagagggga caaagacgtg cactcaacct tctaccaggc						627
cactctcagg ctacacctaa aatcagccct tgatccatt tctgggcaat ttagacagt						687
aaactgactt tgtttacctg cttgcagcat attagaacag acgatccatg ctaatatgt						747
atttttctctt aaaacatagc tttcctgtaa tttaaagtgc ttttatgaaa atatttgtaa						807
ttaattatat atagttggaa atagcagtaa gctttcccat tataatatat ttttggtatac						867
aaataaaaatt tgaactgaac ctctgtgcc						895

<210> 78

<211> 117

<212> PRT

<213> NM 014059 RGC32

<400> 78

Met Lys Pro Pro Ala Glu Asp Leu Ser Asp Ala Leu Cys Glu Phe Asp
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Ala Val Leu Ala Asp Phe Ala Ser Pro Phe His Glu Arg His Phe His
 20 25 30

Tyr Glu Glu His Leu Glu Arg Met Lys Arg Arg Ser Ser Ala Ser Val
 35 40 45

Ser Asp Ser Ser Gly Phe Ser Asp Ser Glu Ser Ala Asp Ser Leu Tyr
 50 55 60

Arg Asn Ser Phe Ser Phe Ser Asp Glu Lys Leu Asn Ser Pro Thr Asp
 65 70 75 80

Ser Thr Pro Ala Leu Leu Ser Ala Thr Val Thr Pro Gln Lys Ala Lys
 85 90 95

Leu Gly Asp Thr Lys Glu Leu Glu Ala Phe Ile Ala Asp Leu Asp Lys
 100 105 110

Thr Leu Ala Ser Met
 115

<210> 79

<211> 1564

<212> DNA

<213> NM_018004 FLJ10134

<220>

<221> CDS

<222> (314)..(1138)

<223>

<400> 79

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 acccaagttt aaaaattcct cccccactc aatgcgagac gtggccagat cccatccaac 180
 acacggttta attttcatgg ggctctggga tcaaagaac agaaacagca acaacaaaag 240
 cccagccgct gtctgatttt aagctggcaa agtgggaaaa ataaagtgtt gagtaaacag 300
 accaagttgg atc atg ggg aat ttc aga ggt cat gcc ctc cct gga acc 349
 Met Gly Asn Phe Arg Gly His Ala Leu Pro Gly Thr
 1 5 10

ttc ttt ttt att att ggt ctt tgg tgg tgt aca aag agt att ctg aag Phe Phe Phe Ile Ile Gly Leu Trp Trp Cys Thr Lys Ser Ile Leu Lys 15 20 25	397
tat atc tgc aaa aag caa aag cga acc tgc tat ctt ggt tcc aaa aca Tyr Ile Cys Lys Lys Gln Lys Arg Thr Cys Tyr Leu Gly Ser Lys Thr 30 35 40	445
tta ttc tat cga ttg gaa att ttg gag gga att aca ata gtt ggc atg Leu Phe Tyr Arg Leu Glu Ile Leu Glu Gly Ile Thr Ile Val Gly Met 45 50 55 60	493
gct tta act ggc atg gct ggg gag cag ttt att cct gga ggg ccc cat Ala Leu Thr Gly Met Ala Gly Glu Gln Phe Ile Pro Gly Gly Pro His 65 70 75	541
ctg atg tta tat gac tat aaa caa ggt cac tgg aat caa ctc ctg ggc Leu Met Leu Tyr Asp Tyr Lys Gln Gly His Trp Asn Gln Leu Leu Gly 80 85 90	589
tgg cat cat ttc acc atg tat ttc ttc ttt ggg ctg ttg ggt gtg gca Trp His His Phe Thr Met Tyr Phe Phe Phe Gly Leu Leu Gly Val Ala 95 100 105	637
gat atc tta tgt ttc acc atc agt tca ctt cct gtg tcc tta acc aag Asp Ile Leu Cys Phe Thr Ile Ser Ser Leu Pro Val Ser Leu Thr Lys 110 115 120	685
tta atg ttg tca aat gcc tta ttt gtg gag gcc ttt atc ttc tac aac Leu Met Leu Ser Asn Ala Leu Phe Val Glu Ala Phe Ile Phe Tyr Asn 125 130 135 140	733
cac act cat ggc cgg gaa atg ctg gac atc ttt gtg cac cag ctg ctg His Thr His Gly Arg Glu Met Leu Asp Ile Phe Val His Gln Leu Leu 145 150 155	781
gtt ttg gtc gtc ttt ctg aca ggc ctc gtt gcc ttc cta gag ttc ctt Val Leu Val Val Phe Leu Thr Gly Leu Val Ala Phe Leu Glu Phe Leu 160 165 170	829
gtt cgg aac aat gta ctt ctg gag cta ttg cgg tca agt ctc att ctg Val Arg Asn Val Leu Leu Glu Leu Leu Arg Ser Ser Leu Ile Leu 175 180 185	877
ctt cag ggg agc tgg ttc ttt cag att gga ttt gtc ctg tat ccc ccc Leu Gln Gly Ser Trp Phe Phe Gln Ile Gly Phe Val Leu Tyr Pro Pro 190 195 200	925
agt gga ggt cct gca tgg gat ctg atg gat cat gaa aat att ttg ttt Ser Gly Gly Pro Ala Trp Asp Leu Met Asp His Glu Asn Ile Leu Phe 205 210 215 220	973
ctc acc ata tgc ttt tgt tgg cat tat gca gta acc att gtc atc gtt Leu Thr Ile Cys Phe Cys Trp His Tyr Ala Val Thr Ile Val Ile Val 225 230 235	1021
gga atg aat tat gct ttc att acc tgg ttg gtt aaa tct aga ctt aag Gly Met Asn Tyr Ala Phe Ile Thr Trp Leu Val Lys Ser Arg Leu Lys 240 245 250	1069
agg ctc tgc tcc tca gaa gtt gga ctt ctg aaa aat gct gaa cga gaa Arg Leu Cys Ser Ser Glu Val Gly Leu Leu Lys Asn Ala Glu Arg Glu 255 260 265	1117
caa gaa tca gaa gaa gaa atg tgactttgat gagcttccag tttttctaga Gln Glu Ser Glu Glu Glu Met 270 275	1168

taaacctttt cttttttaca ttgttcttgg ttttgtttct cgatcttttg tttggagaac 1228
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 aatttaaata ttttcttttt agctttgaaa atattttggg tgatactttc attttgcaca 1348
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<210> 80

<211> 275

<212> PRT

<213> NM_018004 FLJ10134

<400> 80

Met Gly Asn Phe Arg Gly His Ala Leu Pro Gly Thr Phe Phe Phe Ile
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Ile Gly Leu Trp Trp Cys Thr Lys Ser Ile Leu Lys Tyr Ile Cys Lys
 20 25 30

Lys Gln Lys Arg Thr Cys Tyr Leu Gly Ser Lys Thr Leu Phe Tyr Arg
 35 40 45

Leu Glu Ile Leu Glu Gly Ile Thr Ile Val Gly Met Ala Leu Thr Gly
 50 55 60

Met Ala Gly Glu Gln Phe Ile Pro Gly Gly Pro His Leu Met Leu Tyr
 65 70 75 80

Asp Tyr Lys Gln Gly His Trp Asn Gln Leu Leu Gly Trp His His Phe
 85 90 95

Thr Met Tyr Phe Phe Phe Gly Leu Leu Gly Val Ala Asp Ile Leu Cys
 100 105 110

Phe Thr Ile Ser Ser Leu Pro Val Ser Leu Thr Lys Leu Met Leu Ser
 115 120 125

Asn Ala Leu Phe Val Glu Ala Phe Ile Phe Tyr Asn His Thr His Gly
 130 135 140

Arg Glu Met Leu Asp Ile Phe Val His Gln Leu Leu Val Leu Val Val
 145 150 155 160

Phe Leu Thr Gly Leu Val Ala Phe Leu Glu Phe Leu Val Arg Asn Asn
 165 170 175

Val Leu Leu Glu Leu Leu Arg Ser Ser Leu Ile Leu Leu Gln Gly Ser
 180 185 190

Trp Phe Phe Gln Ile Gly Phe Val Leu Tyr Pro Pro Ser Gly Gly Pro
 195 200 205

Ala Trp Asp Leu Met Asp His Glu Asn Ile Leu Phe Leu Thr Ile Cys
 210 215 220

Phe Cys Trp His Tyr Ala Val Thr Ile Val Ile Val Gly Met Asn Tyr
 225 230 235 240

Ala Phe Ile Thr Trp Leu Val Lys Ser Arg Leu Lys Arg Leu Cys Ser
 245 250 255

Ser Glu Val Gly Leu Leu Lys Asn Ala Glu Arg Glu Gln Glu Ser Glu
 260 265 270

Glu Glu Met
 275

<210> 81

<211> 2311

<212> DNA

<213> NM_004004 GJB2, connexin 26

<220>

<221> CDS

<222> (199)..(876)

<223>

<400> 81

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gtctccctgt tctgtcctag ctatgttcct gtgttggtg cattcgtctt ttccagagca 180

aaccgcccag agtagaag atg gat tgg ggc acg ctg cag acg atc ctg ggg 231
 Met Asp Trp Gly Thr Leu Gln Thr Ile Leu Gly
 1 5 10

ggt gtg aac aaa cac tcc acc agc att gga aag atc tgg ctc acc gtc 279
 Gly Val Asn Lys His Ser Thr Ser Ile Gly Lys Ile Trp Leu Thr Val
 15 20 25

ctc ttc att ttt cgc att atg atc ctc gtt gtg gct gca aag gag gtg 327

Leu Phe Ile Phe Arg Ile Met Ile Leu Val Val Ala Ala Lys Glu Val	
30 35 40	
tgg gga gat gag cag gcc gac ttt gtc tgc aac acc ctg cag cca ggc	375
Trp Gly Asp Glu Gln Ala Asp Phe Val Cys Asn Thr Leu Gln Pro Gly	
45 50 55	
tgc aag aac gtg tgc tac gat cac tac ttc ccc atc tcc cac atc cgg	423
Cys Lys Asn Val Cys Tyr Asp His Tyr Phe Pro Ile Ser His Ile Arg	
60 65 70 75	
cta tgg gcc ctg cag ctg atc ttc gtg tcc agc cca gcg ctc cta gtg	471
Leu Trp Ala Leu Gln Leu Ile Phe Val Ser Ser Pro Ala Leu Leu Val	
80 85 90	
gcc atg cac gtg gcc tac cgg aga cat gag aag aag agg aag ttc atc	519
Ala Met His Val Ala Tyr Arg Arg His Glu Lys Lys Arg Lys Phe Ile	
95 100 105	
aag ggg gag ata aag agt gaa ttt aag gac atc gag gag atc aaa acc	567
Lys Gly Glu Ile Lys Ser Glu Phe Lys Asp Ile Glu Glu Ile Lys Thr	
110 115 120	
cag aag gtc cgc atc gaa gcc tcc ctg tgg tgg acc tac aca agc agc	615
Gln Lys Val Arg Ile Glu Gly Ser Leu Trp Trp Thr Tyr Thr Ser Ser	
125 130 135	
atc ttc ttc cgg gtc atc ttc gaa gcc gcc ttc atg tac gtc ttc tat	663
Ile Phe Phe Arg Val Ile Phe Glu Ala Ala Phe Met Tyr Val Phe Tyr	
140 145 150 155	
gtc atg tac gac gcc ttc tcc atg cag cgg ctg gtg aag tgc aac gcc	711
Val Met Tyr Asp Gly Phe Ser Met Gln Arg Leu Val Lys Cys Asn Ala	
160 165 170	
tgg cct tgt ccc aac act gtg gac tgc ttt gtg tcc cgg ccc acg gag	759
Trp Pro Cys Pro Asn Thr Val Asp Cys Phe Val Ser Arg Pro Thr Glu	
175 180 185	
aag act gtc ttc aca gtg ttc atg att gca gtg tct gga att tgc atc	807
Lys Thr Val Phe Thr Val Phe Met Ile Ala Val Ser Gly Ile Cys Ile	
190 195 200	
ctg ctg aat gtc act gaa ttg tgt tat ttg cta att aga tat tgt tct	855
Leu Leu Asn Val Thr Glu Leu Cys Tyr Leu Leu Ile Arg Tyr Cys Ser	
205 210 215	
ggg aag tca aaa aag cca gtt taacgcattg ccagttgtt agattaagaa	906
Gly Lys Ser Lys Lys Pro Val	
220 225	
atagacagca tgagagggat gaggaacccc gtgctcagct gtcaaggctc agtcgccagc	966
atttcccaac acaaagattc tgaccttaaa tgcaaccatt tgaaaccctt gtaggcctca	1026
ggtgaaactc cagatgccac aatgagctct gctcccctaa agcctcaaaa caaaggccta	1086
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ttacactttt tggaagtgaa aactttgtag tatgataggt tattttgatg taaagatgtt	1446

ctggatacca ttatatgttc ccctgtttc agaggctcag attgtaatat gtaaattgga 1506
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 tgtttggtt acccccttca gcctccaatt ttttaagtga aaatataact aataacatgt 2046
 gaaaagaata gaagctaagg tttagataaa tattgagcag atctatagga agattgaacc 2106
 tgaatattgc cattatgctt gacatggtt ccaaaaaatg gtactccaca tacttcagtg 2166
 agggtaagta ttttctgtt gtcaagaata gcattgtaaa agcattttgt aataataaag 2226
 aatagcttta atgatatgct tgtaactaaa ataattttgt aatgtatcaa atacatttaa 2286
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<210> 82

<211> 226

<212> PRT

<213> NM_004004 GJB2, connexin 26

<400> 82

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Ser Thr Ser Ile Gly Lys Ile Trp Leu Thr Val Leu Phe Ile Phe Arg
20 25 30

Ile Met Ile Leu Val Val Ala Ala Lys Glu Val Trp Gly Asp Glu Gln
35 40 45

Ala Asp Phe Val Cys Asn Thr Leu Gln Pro Gly Cys Lys Asn Val Cys
50 55 60

Tyr Asp His Tyr Phe Pro Ile Ser His Ile Arg Leu Trp Ala Leu Gln
65 70 75 80

Leu Ile Phe Val Ser Ser Pro Ala Leu Leu Val Ala Met His Val Ala
85 90 95

Tyr Arg Arg His Glu Lys Lys Arg Lys Phe Ile Lys Gly Glu Ile Lys
 100 105 110

Ser Glu Phe Lys Asp Ile Glu Glu Ile Lys Thr Gln Lys Val Arg Ile
 115 120 125

Glu Gly Ser Leu Trp Trp Thr Tyr Thr Ser Ser Ile Phe Phe Arg Val
 130 135 140

Ile Phe Glu Ala Ala Phe Met Tyr Val Phe Tyr Val Met Tyr Asp Gly
 145 150 155 160

Phe Ser Met Gln Arg Leu Val Lys Cys Asn Ala Trp Pro Cys Pro Asn
 165 170 175

Thr Val Asp Cys Phe Val Ser Arg Pro Thr Glu Lys Thr Val Phe Thr
 180 185 190

Val Phe Met Ile Ala Val Ser Gly Ile Cys Ile Leu Leu Asn Val Thr
 195 200 205

Glu Leu Cys Tyr Leu Leu Ile Arg Tyr Cys Ser Gly Lys Ser Lys Lys
 210 215 220

Pro Val
 225

<210> 83

<211> 2389

<212> DNA

<213> NM_002514 NOV1, nephroblastoma overexpressed gene

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<221> CDS

<222> (73)..(1143)

<223>

<400> 83

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 Met Gln Ser Val Gln Ser Thr Ser Phe Cys Leu Arg Lys
 1 5 10

cag tgc ctt tgc ctg acc ttc ctg ctt ctc cat ctc ctg gga cag gtc 159
 Gln Cys Leu Cys Leu Thr Phe Leu Leu Leu His Leu Leu Gly Gln Val
 15 20 25

gct gcg act cag cgc tgc cct ccc cag tgc ccg gcc cgg tgc cct gcg 207

Ala Ala Thr Gln Arg Cys Pro Pro Gln Cys Pro Gly Arg Cys Pro Ala	
30 35 40 45	
acg ccg ccg acc tgc gcc ccc ggg gtg cgc gcg gtg ctg gac gcc tgc	255
Thr Pro Pro Thr Cys Ala Pro Gly Val Arg Ala Val Leu Asp Gly Cys	
50 55 60	
tca tgc tgt ctg gtg tgt gcc cgc cag cgt gcc gag agc tgc tca gat	303
Ser Cys Cys Leu Val Cys Ala Arg Gln Arg Gly Glu Ser Cys Ser Asp	
65 70 75	
ctg gag cca tgc gac gag agc agt gcc ctc tac tgt gat cgc agc gcg	351
Leu Glu Pro Cys Asp Glu Ser Ser Gly Leu Tyr Cys Asp Arg Ser Ala	
80 85 90	
gac ccc agc aac cag act gcc atc tgc acg gcg gta gag gga gat aac	399
Asp Pro Ser Asn Gln Thr Gly Ile Cys Thr Ala Val Glu Gly Asp Asn	
95 100 105	
tgt gtg ttc gat ggg gtc atc tac cgc agt gga gag aaa ttt cag cca	447
Cys Val Phe Asp Gly Val Ile Tyr Arg Ser Gly Glu Lys Phe Gln Pro	
110 115 120 125	
agc tgc aaa ttc cag tgc acc tgc aga gat ggg cag att gcc tgt gtg	495
Ser Cys Lys Phe Gln Cys Thr Cys Arg Asp Gly Gln Ile Gly Cys Val	
130 135 140	
ccc cgc tgt cag ctg gat gtg cta ctg cct gag cct aac tgc cca gct	543
Pro Arg Cys Gln Leu Asp Val Leu Leu Pro Glu Pro Asn Cys Pro Ala	
145 150 155	
cca aga aaa gtt gag gtg cct gga gag tgc tgt gaa aag tgg atc tgt	591
Pro Arg Lys Val Glu Val Pro Gly Glu Cys Cys Glu Lys Trp Ile Cys	
160 165 170	
ggc cca gat gag gag gat tca ctg gga gcc ctt acc ctt gca gct tac	639
Gly Pro Asp Glu Glu Asp Ser Leu Gly Gly Leu Thr Leu Ala Ala Tyr	
175 180 185	
agg cca gaa gcc acc cta gga gta gaa gtc tct gac tca agt gtc aac	687
Arg Pro Glu Ala Thr Leu Gly Val Glu Val Ser Asp Ser Ser Val Asn	
190 195 200 205	
tgc att gaa cag acc aca gag tgg aca gca tgc tcc aag agc tgt ggt	735
Cys Ile Glu Gln Thr Thr Glu Trp Thr Ala Cys Ser Lys Ser Cys Gly	
210 215 220	
atg ggg ttc tcc acc cgg gtc acc aat agg aac cgt caa tgt gag atg	783
Met Gly Phe Ser Thr Arg Val Thr Asn Arg Asn Arg Gln Cys Glu Met	
225 230 235	
ctg aaa cag act cgg ctc tgc atg gtg cgg ccc tgt gaa caa gag cca	831
Leu Lys Gln Thr Arg Leu Cys Met Val Arg Pro Cys Glu Gln Glu Pro	
240 245 250	
gag cag cca aca gat aag aaa gga aaa aag tgt ctc cgc acc aag aag	879
Glu Gln Pro Thr Asp Lys Lys Gly Lys Lys Cys Leu Arg Thr Lys Lys	
255 260 265	
tca ctc aaa gcc atc cac ctg cag ttc aag aac tgc acc agc ctg cac	927
Ser Leu Lys Ala Ile His Leu Gln Phe Lys Asn Cys Thr Ser Leu His	
270 275 280 285	
acc tac aag ccc agg ttc tgt ggg gtc tgc agt gat gcc cgc tgc tgc	975
Thr Tyr Lys Pro Arg Phe Cys Gly Val Cys Ser Asp Gly Arg Cys Cys	
290 295 300	
act ccc cac aat acc aaa acc atc cag gca gag ttt cag tgc tcc cca	1023

Thr	Pro	His	Asn	Thr	Lys	Thr	Ile	Gln	Ala	Glu	Phe	Gln	Cys	Ser	Pro		
			305					310					315				
ggg	caa	ata	gtc	aag	aag	cca	gtg	atg	gtc	att	ggg	acc	tgc	acc	tgt		1071
Gly	Gln	Ile	Val	Lys	Lys	Pro	Val	Met	Val	Ile	Gly	Thr	Cys	Thr	Cys		
		320					325					330					
cac	acc	aac	tgt	cct	aag	aac	aat	gag	gcc	ttc	ctc	cag	gag	ctg	gag		1119
His	Thr	Asn	Cys	Pro	Lys	Asn	Asn	Glu	Ala	Phe	Leu	Gln	Glu	Leu	Glu		
	335					340					345						
ctg	aag	act	acc	aga	ggg	aaa	atg	taacctatca	ctcaagaagc	acacctacag							1173
Leu	Lys	Thr	Thr	Arg	Gly	Lys	Met										
350					355												
agc	acctgta	gctgctgcgc	cacccacat	caaaggaata	taagaaaagt	aatgaagaat											1233
cac	gatttca	tccttgaatc	ctatgtat	ttt	tcctaatgtg	atcatatgag	gacctttcat										1293
atc	gtctctt	tatttaacaa	aaaatgtaat	taactgtaaa	cttggaatca	aggtaagctc											1353
agg	atatggc	ttaggaatga	cttactttcc	tgtggtttta	ttacaaatgc	aaatttctat											1413
aaatt	taaga	aaacaagtat	ataatttact	ttgtagactg	tttcacattg	cactcatcat											1473
at	ttt	gtttgt	gcactagtgc	aattccaaga	aaatatcact	gtaatgagtc	agtgaagtct										1533
aga	atc	atac	tttc	attgtacaag	tattacaacc	atatattgag	gttcattggg										1593
aag	attctct	attggctccc	ttttgggta	aaccagctct	gaacttccaa	gctccaaatc											1653
caagg	aaaca	tcagctctt	caacatgaca	tccagagatg	actattactt	ttctgtttag											1713
tttt	actacta	ggaacgtgt	tgtatctaca	gtaatgaaat	gtttactaag	tggactggtg											1773
tcataa	actt	tctccattta	agacacattg	actcctttcc	aatagaaaga	aactaaacag											1833
aaaact	ccca	atacaaagat	gactgggtccc	tcatagccct	cagacattta	tatattggaa											1893
gctgctg	agg	cccccaagtt	ttttaattaa	gcagaaacag	catattagca	gggattctct											1953
catc	taactg	atgagtaa	atgagtaaac	tgaggcccaa	agcacttgct	tacatcctct	gatagctggt										2013
tcaa	atgtgc	at	ttt	gtgga	at	tttgagaa	aaatagagca	aaatcaacat	gactgggtggt								2073
gagag	accac	acattttatg	agagtttgga	attattgtag	acatgcccaa	aacttatcct											2133
tggg	ccataa	ttatgaaaac	tcatgatcaa	gatatatgtg	tatacataca	tgtatctggt											2193
ttgtc	aggct	acaaggtagg	ctgcaaaatt	aaatctagac	attcttttaa	tgccaccaca											2253
cgtgt	ccgc	ttctctcttt	taaagtattt	ataaaatat	aaattgtaca	ttttgtaaaa											2313
tattat	gttt	gatttctcta	cttgtcatat	cactaaataa	acacgatttt	attgctgaaa											2373
aaaaaaaa	aaaaaa																2389

<210> 84

<211> 357

<212> PRT

<213> NM_002514 NOV1, nephroblastoma overexpressed gene

215

<400> 84

Met Gln Ser Val Gln Ser Thr Ser Phe Cys Leu Arg Lys Gln Cys Leu
1 5 10 15

Cys Leu Thr Phe Leu Leu Leu His Leu Leu Gly Gln Val Ala Ala Thr
20 25 30

Gln Arg Cys Pro Pro Gln Cys Pro Gly Arg Cys Pro Ala Thr Pro Pro
35 40 45

Thr Cys Ala Pro Gly Val Arg Ala Val Leu Asp Gly Cys Ser Cys Cys
50 55 60

Leu Val Cys Ala Arg Gln Arg Gly Glu Ser Cys Ser Asp Leu Glu Pro
65 70 75 80

Cys Asp Glu Ser Ser Gly Leu Tyr Cys Asp Arg Ser Ala Asp Pro Ser
85 90 95

Asn Gln Thr Gly Ile Cys Thr Ala Val Glu Gly Asp Asn Cys Val Phe
100 105 110

Asp Gly Val Ile Tyr Arg Ser Gly Glu Lys Phe Gln Pro Ser Cys Lys
115 120 125

Phe Gln Cys Thr Cys Arg Asp Gly Gln Ile Gly Cys Val Pro Arg Cys
130 135 140

Gln Leu Asp Val Leu Leu Pro Glu Pro Asn Cys Pro Ala Pro Arg Lys
145 150 155 160

Val Glu Val Pro Gly Glu Cys Cys Glu Lys Trp Ile Cys Gly Pro Asp
165 170 175

Glu Glu Asp Ser Leu Gly Gly Leu Thr Leu Ala Ala Tyr Arg Pro Glu
180 185 190

Ala Thr Leu Gly Val Glu Val Ser Asp Ser Ser Val Asn Cys Ile Glu
195 200 205

Gln Thr Thr Glu Trp Thr Ala Cys Ser Lys Ser Cys Gly Met Gly Phe
210 215 220

Ser Thr Arg Val Thr Asn Arg Asn Arg Gln Cys Glu Met Leu Lys Gln
225 230 235 240

Thr Arg Leu Cys Met Val Arg Pro Cys Glu Gln Glu Pro Glu Gln Pro
245 250 255

Thr Asp Lys Lys Gly Lys Lys Cys Leu Arg Thr Lys Lys Ser Leu Lys
260 265 270

Ala Ile His Leu Gln Phe Lys Asn Cys Thr Ser Leu His Thr Tyr Lys
275 280 285

Pro Arg Phe Cys Gly Val Cys Ser Asp Gly Arg Cys Cys Thr Pro His
290 295 300

Asn Thr Lys Thr Ile Gln Ala Glu Phe Gln Cys Ser Pro Gly Gln Ile
305 310 315 320

Val Lys Lys Pro Val Met Val Ile Gly Thr Cys Thr Cys His Thr Asn
325 330 335

Cys Pro Lys Asn Asn Glu Ala Phe Leu Gln Glu Leu Glu Leu Lys Thr
340 345 350

Thr Arg Gly Lys Met
355

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU03/01166

A. CLASSIFICATION OF SUBJECT MATTER												
Int. Cl. ⁷ : C12Q 1/68, G01N 33/53												
According to International Patent Classification (IPC) or to both national classification and IPC												
B. FIELDS SEARCHED												
Minimum documentation searched (classification system followed by classification symbols) SEE BELOW												
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched SEE BELOW												
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) DGENE, EMBL, GENBANK: SEQ ID NOS 1-7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 60-63, 65, 67, 69, 71-75, 77, 79, 81, 83 WPIDS: ovarian, cancer, tumour, detect, diagnose												
C. DOCUMENTS CONSIDERED TO BE RELEVANT												
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.										
X	Weitzel JN et al (1994) Gynecologic Oncology 55, pages 245-252 "Molecular genetic changes associated with ovarian cancer" and GENBANK ACC M62397 See table 3 and pages 249 and 50 with respect to SEQ ID NOS 3, 4 (MCC)	1-5, 7, 9-12, 16-20, 22, 24-27, 31-43, 62-69										
X	DGENE Abstract Accession No ABQ54626 & WO 02 00677 A1 (HUMAN GENOME SCIENCES, INC.) 3 January 2002 See abstract and claim 1; SEQ ID NO 506 (applicant's SEQ ID NO 9)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 60-69										
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C <input checked="" type="checkbox"/> See patent family annex												
<p>* Special categories of cited documents:</p> <table border="0"> <tr> <td>"A" document defining the general state of the art which is not considered to be of particular relevance</td> <td>"T" later document published after the international filing date, or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</td> </tr> <tr> <td>"E" earlier application or patent but published on or after the international filing date</td> <td>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</td> </tr> <tr> <td>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</td> <td>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</td> </tr> <tr> <td>"O" document referring to an oral disclosure, use, exhibition or other means</td> <td>"&" document member of the same patent family</td> </tr> <tr> <td>"P" document published prior to the international filing date but later than the priority date claimed</td> <td></td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date, or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family	"P" document published prior to the international filing date but later than the priority date claimed	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date, or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention											
"E" earlier application or patent but published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone											
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art											
"O" document referring to an oral disclosure, use, exhibition or other means	"&" document member of the same patent family											
"P" document published prior to the international filing date but later than the priority date claimed												
Date of the actual completion of the international search 23 October 2003		Date of mailing of the international search report 06 NOV 2003										
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaaustralia.gov.au Facsimile No. (02) 6285 3929		Authorized officer TERRY MOORE Telephone No : (02) 6283 2632										

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU03/01166

C (Continuation 1). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Hough CD et al (2000) Cancer Research 60, 6281-7 "Large-scale serial analysis of gene expression reveals genes differentially expressed in ovarian cancer" See table 3: mal2, claudin 3(relevant to SEQ ID NOs 11, 15)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 60-69
PX	WO 02 071928 A2 (MILLENNIUM PHARMACEUTICALS, INC) 19 September 2002 See table 1 pg 20 KIAA0869: pg 19 FLJ22252: pg 21 SLP1, pgs 21, 24, 25 PAX8: pg 18 ANXA2 (applicant's SEQ ID NOs 13, 17, 25, 43 and 71/72) & DGENE Accession No ABS76418 (applicant's SEQ ID NO 17)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47-53, 60-69
PX	WO 02 102235 A2 (EOS BIOTECHNOLOGY, INC) 27 December 2002 See pg 187 KIAA0869: pg 184 claudin 7: pgs 111, 162 and 180 KIAA0101: pg 120 KIAA1481, pgs 152, 174, 184, 202 paired box gene 8: pgs 155, 161 methylene tetrahydrofolate dehydrogenase: pg 176 DD5: pg 125 SOCS3: pg 261 serum amyloid A1 (applicant's SEQ ID NOs 13, 21, 23, 37, 43, 55, 63, 73/74 and 75)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47-53, 60-69
PX	DGENE Abstract Accession No ACA66405 & US 2003/0004102 A1 (ASHKENAZI AJ et al) 2 January 2003 See abstract and claim 2, figure 203 (applicant's SEQ ID NO 19)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 60-69
X	Scheurle D et al "Cancer gene discovery using digital differential display" (2000)(online), (retrieved on 16 October 2003) Retrieved from Internet<URL:http://www.fau.edu/cmhb/publications/cancergenes.htm> See "up-regulation of known genes: claudin 7, secreted frizzled rel. pro. 4 (applicant's SEQ ID NOs 21 and 69)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47-53, 60-69
X	DGENE Abstract Accession No AAS56533 & WO 01 70796 A2 (CORIXA CORPORATION) 27 September 2001 See abstract and claim 1, page 165 KIAA0101 (applicant's SEQ ID NO 23)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 60-69
X	Medline Abstract 11906548 Shigemasa K et al (2001) Int J Gynecol Cancer 11(6), 454-61 "Expression of the protease inhibitor antileukoprotease and the serine protease stratum corneum chymotryptic enzyme (SCCE) is coordinated in ovarian tumours" See abstract, relevant to applicant's SEQ ID NO 25	1-5, 7, 9-11, 16-20, 22, 25-27, 31-42, 62-69

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU03/01166

C (Continuation 2)

DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Laval S et al (1994) Cell Growth Differ 5(11), 1173-83 "Isolation and characterization of an epithelial-specific receptor tyrosine kinase from an ovarian cancer cell line" See whole document, relevant to applicant's SEQ ID NO 27	1-5, 7, 9-11, 16-20, 22, 25- 27, 31-42, 62- 69
PX	WO 03 068054 A2 (THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by THE SECRETARY, DEPARTMENT OF HEALTH SERVICES) 21 August 2003 See in particular table 1, pg 22/60 EDDR1: pg 32/60 TOP2A: 29/60 PAX8 and 33/60 SFRP4 (applicant's SEQ ID NOs 27, 29, 43 and 69)	1-5, 7, 10-12, 16-20, 22, 25- 27, 31-43, 45, 47, 51-53, 62- 69
X	Koshiyama M et al (2001) Anticancer Res 21, 2925-32 "Immunohistochemical expression of topoisomerase II alpha (TopII alpha) and multidrug resistance-associated protein (MRP), plus chemosensitivity testing, as chemotherapeutic indices of ovarian endometrial carcinomas" See whole document, relevant to applicant's SEQ ID NO 29	1-5, 7, 10-12, 16-20, 22, 26, 27, 31-40, 42, 43, 62-69
X	Gotlieb WH et al (2001) Gynecol Oncol 82(1), 99-104 "Topoisomerase II immunostaining as a prognostic marker for survival in ovarian cancer" See whole document, relevant to applicant's SEQ ID NO 29	1-5, 7, 10-12, 16-20, 22, 26, 27, 31-40, 42, 43, 62-69
X	Costa MJ et al (2000) Int J Gynecol Pathol 19(3), 248-57 "Topoisomerase II alpha: prognostic predictor and cell cycle marker in surface epithelial neoplasms of the ovary and peritoneum" See whole document, relevant to applicant's SEQ ID NO 29	1-5, 7, 10-12, 16-20, 22, 25- 27, 31-43, 62- 69
X	DGENE Abstract Accession No ABQ54317 & WO 02 00677 A1 (HUMAN GENOME SCIENCES, INC.) 3 January 2002 See abstract and claim 1, SEQ ID NO 197 (applicant's SEQ ID NO 31 reverse complement)	1-5, 7, 10-12, 16-20, 22, 25- 27, 31-43, 60- 69
PX	DGENE Abstract Accession No ACA03948 & US 2002/0192678 A1 (CHEN H-M) 19 December 2002 See abstract and example 13, pages 98-99 (applicant's SEQ ID NO 33)	1-5, 7, 10-12, 16-20, 22, 24- 27, 31-43, 62- 69

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU03/01166

C (Continuation 3) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Medline Abstract 11925933 Sakamoto M et al (2001) Hum Cell 14(4), 305-15 "Analysis of gene expression profiles associated with cisplatin resistance in human ovarian cancer cell lines and tissues using cDNA microarray" See whole document, relevant to applicant's SEQ ID NO 35	1-5, 7, 10-12, 16-20, 22, 24- 27, 31-43, 62- 69
X	DGENE Abstract Accession No ABQ54876 & WO 02 00677 A1 (HUMAN GENOME SCIENCES, INC.) 3 January 2002 See abstract and claim 1, SEQ ID NO 756 (applicant's SEQ ID NO 39)	1-5, 7, 10-12, 16-20, 22, 25- 27, 31-43, 60- 69
X	DGENE Abstract Accession No ABL83226 & WO 01 92581 A2 (CORIXA CORPORATION) 6 December 2001 See abstract and claim 1, SEQ ID NO 6204 (applicant's SEQ ID NO 41)	1-5, 7, 10-12, 16-20, 22, 25- 27, 31-43, 60- 69
X	Genbank Accession No AK075046 3 September 2002 Isogai T et al <i>Homo sapiens</i> cDNA FLJ90565, clone OVARC1001336 See "features" (applicant's SEQ ID NO 50)	1-5, 7, 16-20, 22, 31-40, 62- 67
X	DGENE Abstract Accession No AAH83197 & WO 01 51513 A2 (CORIXA CORPORATION) 19 July 2001 See abstract and claim 5, SEQ ID NO 821 (applicant's SEQ ID NO 52)	1-5, 7, 10-12, 16-20, 22, 25- 27, 31-43, 60- 69
X	DGENE Abstract Accession No ABL90699 & WO 01 90304 A2 (HUMAN GENOME SCIENCES) 29 November 2001 See abstract and claim 4, SEQ ID NO 1261 (applicant's SEQ ID NO 53)	1-5, 7, 10-12, 16-20, 22, 25- 27, 31-43, 60- 69
X	DGENE Abstract Accession No AAZ77553 & WO 99 53040 A2 (METAGEN GESELLSCHAFT F R GENOMFORSHUNG) 21 October 1999 See abstract, claim 3 and page 226 (applicant's SEQ ID NO 57)	1-5, 7, 10-12, 15-20, 22, 25- 27, 30-43, 60- 69
X	DGENE Abstract Accession No ABL67667 & WO 01 94629 A2 (AVALON PHARMACEUTICALS) 13 December 2001 See abstract and claim 1, SEQ ID NO 6004 (applicant's SEQ ID NOs 59, 60)	1-5, 7, 10-12, 15-20, 22, 25- 27, 30-43, 60- 69

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU03/01166

C (Continuation 4) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DGENE Abstract Accession No ABL61830 & WO 01 94629 A2 (AVALON PHARMACEUTICALS) 13 December 2001 See abstract and claim 1, SEQ ID NO 167 (applicant's SEQ ID NOs 61, 62)	1-5, 7, 10-12, 15-20, 22, 24-27, 30-43, 62-69
X	DGENE Abstract Accession No AAV64871 & WO 98 48010 A1 (GARVAN INSTITUTE OF MEDICAL RESEARCH) 29 October 1998 See Abstract and figure 3B, example and pg 22 line 34 of WO 98 48010 (applicant's SEQ ID NO 63)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47, 51-53, 60-69
X	DGENE Abstract Accession No ABV34360 & WO 01 60860 A2 (MILLENNIUM PREDICTIVE MEDICINE, INC) 23 August 2001 See Abstract, claim 1, pg 19 and pg 7222 (applicant's SEQ ID NO 65)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47, 51-53, 60-69
X	DGENE Abstract Accession No ABQ54583 & WO 02 00677 A1 (HUMAN GENOME SCIENCES, INC.) 3 January 2002 See in particular abstract and claim 1, SEQ ID NO 463 (applicant's SEQ ID NO 67)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47, 51-53, 60-69
X	DGENE Abstract Accession No ABL62031 & WO 01 94629 A2 (AVALON PHARMACEUTICALS) 13 December 2001 See abstract and claim 1, SEQ ID NO 368 (applicant's SEQ ID NOs 73, 74)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47-53, 60-69
X	DGENE Abstract Accession No AAI99253 & WO 01 55313 A2 (HUMAN GENOME SCIENCES, INC) 2 August 2001 See abstract, example 2 and SEQ ID NO 1017 (applicant's SEQ ID NO 77)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47, 51-53, 60-69
X	DGENE Abstract Accession No ABL64081 & WO 01 94629 A2 (AVALON PHARMACEUTICALS) 13 December 2001 See abstract and claim 1, SEQ ID NO 2418 (applicant's SEQ ID NO 79)	1-5, 7, 10-12, 16-20, 22, 25-27, 31-43, 45, 47-53, 60-69

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU03/01166

C (Continuation 5) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DGENE Abstract Accession No ABL66499 & WO 01 94629 A2 (AVALON PHARMACEUTICALS) 13 December 2001 See abstract and claim 1, SEQ ID NO 4836 (applicant's SEQ ID NO 81)	1-5, 7, 10-12, 16-20, 22, 24- 27, 31-43, 45, 47, 51-53, 60- 69

INTERNATIONAL SEARCH REPORT

International application No.
PCT/AU03/01166

Box I Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos : 70-73
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The claims are not limited to the technical features of the invention as disclosed in, and supported by, the specification. The claims relate to methods of assessing the promoter regions of specific genes with respect to hypermethylation and ovarian cancer. However the specification only discloses sequences derived from cDNA clones and does not disclose any promoter sequences.

3. ☐ Claims Nos :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See supplementary sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:2-5, 7, 9, 15, 19, 20, 22, 24, 30, 45 and 47-50 in full and claims 1, 10-12, 16-18, 25-27, 31-43, 51-53 and 60-69 as they relate to table 3.

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant's protest.
☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/AU03/01166

Supplemental Box

(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: II

The application claims more than one invention. Rule 13.1 of the PCT states the principle that an International Application should relate to only one invention or, if there is more than one invention, that the inclusion of those inventions in one International Application is only permitted if all inventions are so linked as to form a single general inventive concept.

Rule 13.2 of the PCT defines the method for determining whether the requirement of unity of invention is satisfied in respect of a group of inventions claimed in an International application. Unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding "special technical features." The expression "special technical features" is defined in Rule 13.2 as meaning those technical features that define a contribution which each of the inventions, considered as a whole, makes over the prior art. The determination is made on the contents of the claims as interpreted in light of the description and drawings (if any).

The claims and the description relate to methods for the diagnosis, prediction and treatment of ovarian cancer, using gene and peptide sequences whose expression is altered in ovarian cancer. In particular the claims define methods relating to the use of over 693 specific gene and/or peptide sequences.

Although all of the claims share the common feature that they all relate to methods or apparatus that involve the use of specific gene or peptide sequences whose expression is altered in ovarian cancer, this feature is known (see the documents listed below). As such this feature cannot be regarded as a special technical feature and cannot confer unity on the inventions relating to the use of specific gene or peptide sequences for the detection or treatment of ovarian cancer.

D1 US 5 912 142

D2 US 6 268 165

D3 WO 01 21653

D4 Bayani et al (2002) Cancer Research 62, 3466-76

Furthermore, there is nothing in the specification to suggest that the genes can be further divided into groups, where sequences within a group share a common special technical feature. Although the specification discloses that some of the genes can be classified into further, narrower groups, these further divisions also cannot be regarded as special technical features. These divisions correspond to groups of genes that are down-regulated or up-regulated in cancers and genes that are associated with specific types of ovarian cancers, such as epithelial or mucinous ovarian cancer. However these groups are known, as are methods of using genes specifically associated with these narrower groups for the treatment and detection of specific subsets of ovarian cancers. See in particular D4

Although there is a lack of unity the ISA has searched, as a service to the applicant, five sets of ten sequences for five search fees.

These sequences comprise SEQ ID NOS 1- 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 46, 48, 50, 52, 53, 55, 57, 59, 60- 63, 65, 67, 69, 71-75, 77, 79, 81, 83.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/AU03/01166

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member			
WO	0200677	AU	29508/01	AU	30958/01
		AU	36460/01	AU	36461/01
		AU	36463/01	AU	36464/01
		AU	36466/01	AU	37943/01
		AU	37947/01	AU	37949/01
		AU	37951/01	AU	37952/01
		AU	37954/01	AU	37955/01
		AU	37958/01	AU	38585/01
		AU	39727/01	AU	39728/01
		AU	41403/01	AU	41404/01
		AU	41406/01	AU	41407/01
		AU	41409/01	AU	41410/01
		AU	41412/01	AU	41413/01
		AU	41415/01	AU	41416/01
		AU	41418/01	AU	41419/01
		AU	43135/01	AU	43136/01
		AU	45262/01	AU	45354/01
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		AU	49054/01	AU	50767/01
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		AU	50772/01	AU	52878/01
		AU	55162/01	AU	57912/01
		AU	62899/01	AU	66787/01
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		AU	36459/01	AU	36462/01
		AU	36465/01	AU	37944/01
		AU	37950/01	AU	37953/01
		AU	37957/01	AU	39726/01
		AU	41402/01	AU	41405/01
		AU	41408/01	AU	41411/01
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		AU	43134/01	AU	43137/01
		AU	47190/01	AU	49053/01
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		AU	52879/01	AU	60969/01
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International application No.

PCT/AU03/01166

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Information on patent family members

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PCT/AU03/01166

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INTERNATIONAL SEARCH REPORT
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PCT/AU03/01166

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PCT/AU03/01166

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INTERNATIONAL SEARCH REPORT
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INTERNATIONAL SEARCH REPORT

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INTERNATIONAL SEARCH REPORT
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PCT/AU03/01166

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INTERNATIONAL SEARCH REPORT

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PCT/AU03/01166

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/AU03/01166

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PCT/AU03/01166

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